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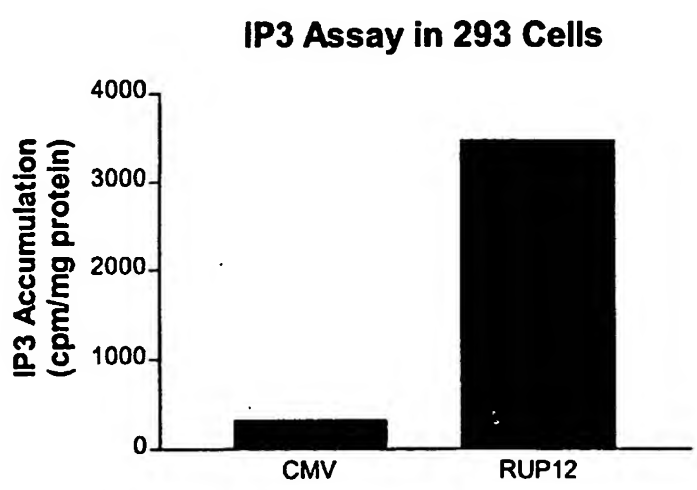
(54) Title: ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS



(57) Abstract: The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

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ENDOGENOUS AND NON-ENDOGENOUS VERSIONS OF HUMAN G PROTEIN-COUPLED RECEPTORS

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to human G protein-coupled receptors, and specifically to endogenous human GPCRs with particular emphasis 'on non-endogenous versions of the GPCRs that have been altered to establish or enhance constitutive activity of the receptor. Preferably, the altered GPCRs are used for the direct identification of candidate compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents.

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2%, or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, approximately 60% of all prescription pharmaceuticals have been developed.

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.,* transmembrane-1 (TM-1), transmebrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3,

transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.,* that a GPCR can interact with more than one G protein. *See*, Kenakin, T., 43 *Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition. It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction pathway to produce a biological response. Changing the receptor

conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or a compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than endogenous ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by simulating the effect of an endogenous ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

SUMMARY OF THE INVENTION

Disclosed herein are endogenous and non-endogenous versions of human GPCRs and uses thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides an illustration of second messenger IP_3 production from endogenous version RUP12 ("RUP12") as compared with the control ("CMV").

Figure 2 is a graphic representation of the results of a second messenger cell-based cyclic AMP assay providing comparative results for constitutive signaling of endogenous RUP13 ("RUP13") and a control vector ("CMV").

Figure 3 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP13 ("RUP13 wt") and non-endogenous, constitutively activated RUP13 ("RUP13(A268K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 4 is a graphic representation of the results of a [^{35}S]GTPγS assay providing comparative results for constitutive signaling by RUP13:Gs Fusion Protein ("RUP13-Gs") and a control vector ("CMV").

Figure 5 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP14 ("RUP14 wt") and non-endogenous, constitutively activated RUP13 ("RUP14(L246K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 6 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP15 ("RUP15 wt") and non-endogenous, constitutively activated RUP15 ("RUP15(A398K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 7 is a graphic representation of the results of a second messenger cell-based cyclic AMP assay providing comparative results for constitutive signaling of endogenous RUP15 ("RUP15 wt"), non-endogenous, constitutively activated version of RUP15 ("RUP15(A398K)") and a control vector ("CMV").

Figure 8 is a graphic representation of the results of a [^{35}S]GTPγS assay providing comparative results for constitutive signaling by RUP15:Gs Fusion Protein ("RUP15-Gs") and a control vector ("CMV").

Figure 9 provides an illustration of second messenger IP_3 production from endogenous version RUP17 ("RUP17") as compared with the control ("CMV").

Figure 10 provides an illustration of second messenger IP_3 production from endogenous version RUP21 ("RUP21") as compared with the control ("CMV").

Figure 11 is a diagrammatic representation of the signal measured comparing CMV, endogenous RUP23 ("RUP23 wt") and non-endogenous, constitutively activated RUP23 ("RUP23(W275K)"), utilizing 8XCRE-Luc reporter plasmid.

Figure 12 is a graphic representation of results from a primary screen of several candidate compounds against RUP13; results for "Compound A" are provided in well A2 and "Compound "B" are provided in well G9.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

TABLE A

ALANINE	ALA	A
ARGININE	ARG	R
ASPARAGINE	ASN	N
ASPARTIC ACID	ASP	D
CYSTEINE	CYS	C
GLUTAMIC ACID	GLU	E
GLUTAMINE	GLN	Q
GLYCINE	GLY	G
HISTIDINE	HIS	H
ISOLEUCINE	ILE	I
LEUCINE	LEU	L
LYSINE	LYS	K
METHIONINE	MET	M

PHENYLALANINE	PHE	F
PROLINE	PRO	P
SERINE	SER	S
THREONINE	THR	T
TRYPTOPHAN	TRP	W
TYROSINE	TYR	Y
VALINE	VAL	V

PARTIAL AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean materials (*e.g.*, ligands, candidate compounds) that competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. ANTAGONISTS do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation, a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

COMPOSITION means a material comprising at least one component; a "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

CODON shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to constitutive receptor activation. A constitutively activated receptor can be endogenous or non-endogenous.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

DIRECTLY IDENTIFYING or **DIRECTLY IDENTIFIED**, in relationship to the phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This phrase is, under no circumstances, to be interpreted or understood to be encompassed by or to encompass the phrase "indirectly identifying" or "indirectly identified."

ENDOGENOUS shall mean a material that a mammal naturally produces. ENDOGENOUS in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation, in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and **GPCR FUSION PROTEIN**, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "Gsα" is the predominate G protein that couples with the GPCR, a GPCR Fusion Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to Gsα; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G

protein can be fused directly to the c-terminus of the constitutively active GPCR or there may be spacers between the two.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

INDIRECTLY IDENTIFYING or **INDIRECTLY IDENTIFIED** means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

INHIBIT or **INHIBITING,** in relationship to the term "response" shall mean that a response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean materials (*e.g.*, ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the active form of the receptor below the normal base level of activity which

is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

KNOWN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

MUTANT or **MUTATION** in reference to an endogenous receptor's nucleic acid and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

NON-ORPHAN RECEPTOR shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

SECOND MESSENGER shall mean an intracellular response produced as a result of receptor activation. A second messenger can include, for example, inositol triphosphate (IP_3), diacycglycerol (DAG), cyclic AMP (cAMP), and cyclic GMP (cGMP). Second messenger response can be measured for a determination of receptor activation. In addition, second messenger response can be measured for the direct identification of candidate compounds, including for example, inverse agonists, agonists, partial agonists and antagonists.

STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

A. Introduction

The traditional study of receptors has always proceeded from the a priori assumption (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand. This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

B. Identification of Human GPCRs

The efforts of the Human Genome project has led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of human GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database. Table B, below, lists several endogenous GPCRs that we have discovered, along with other GPCR's that are homologous to the disclosed GPCR.

TABLE B

Disclosed Human Orphan GPCRs	Accession Number Identified	Open Reading Frame (Base Pairs)	Reference To Homologous GPCR	Per Cent Homology To Designated GPCR
hRUP8	AL121755	1,152bp	NPY2R	27%
hRUP9	AC0113375	1,260bp	GAL2R	22%
hRUP10	AC008745	1,014bp	C5aR	40%
hRUP11	AC013396	1,272bp	HM74	36%
hRUP12	AP000808	966bp	Mas1	34%
hRUP13	AC011780	1,356bp	Fish GPRX-ORYLA	43%
hRUP14	AL137118	1,041bp	CysLT1R	35%
hRUP15	AL016468	1,527bp	RE2	30%
hRUP16	AL136106	1,068bp	GLR101	37%
hRUP17	AC023078	969bp	Mas1	37%
hRUP18	AC008547	1,305bp	Oxytocin	31%
hRUP19	AC026331	1,041bp	HM74	52%
hRUP20	AL161458	1,011bp	GPR34	25%
hRUP21	AC026756	1,014bp	P2Y1R	37%
hRUP22	AC027026	993bp	RUP17 Mas1	67% 37%

hRUP23	AC007104	1,092bp	Rat GPR26	31%
hRUP24	AL355388	1,125bp	SALPR	44%
hRUP25	AC026331	1,092bp	HM74	95%
hRUP26	AC023040	1,044bp	Rabbit 5HT1D	27%
hRUP27	AC027643	158,700	MCH	38%

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, we will disclose techniques for mutating these receptors to establish non-endogenous, constitutively activated versions of these receptors.

The techniques disclosed herein have also been applied to other human, orphan GPCRs known to the art, as will be apparent as the patent document progresses.

C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated version of the human GPCRs disclosed herein allows for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. Using routine, and often commercially available techniques, one can determine areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed. It is also possible using these techniques to determine related disease/disorder states which are associated with the expression and/or over-expression of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of the human GPCR disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed in co-pending and commonly assigned patent document PCT Application

Number PCT/US99/23938, published as WO 00/22129 on April 20, 2000, which, along with the other patent documents listed herein, is incorporated herein by reference. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue (or, of course, endogenous constitutive substitutionf for such proline residue). By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue, such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

D. Disease/Disorder Identification and/or Selection

As will be set forth in greater detail below, most preferably inverse agonists and agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this invention. Such inverse agonists and agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. For example, scanning both diseased and normal tissue samples for the presence of the GPCR now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder.

Preferably, the DNA sequence of the human GPCR is used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression of the receptor in tissue samples. The presence of a receptor in a tissue

source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

E. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active, it binds to a G protein (*e.g.*, Gq, Gs, Gi, Gz, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, $[^{35}S]GTP\gamma S$, can be used to monitor enhanced binding to membranes which express constitutively activated receptors. It is reported that $[^{35}S]GTP\gamma S$ can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the

receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. Gs, Gz and Gi.

Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or transcription factor (CREB) that then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β-galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes the accumulation of cAMP that then activates the gene and expression of

the reporter protein. The reporter protein such as β-galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

b. Go and Gq.

Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2, releasing two intracellular messengers: diacycloglycerol (DAG) and inistol 1,4,5-triphoisphate (IP_3). Increased accumulation of IP_3 is associated with activation of Gq- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3[rd] Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP_3 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of IP_3). Gq-associated receptors can also been examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

3. GPCR Fusion Protein

The use of an endogenous, constitutively activate orphan GPCR or a non-endogenous, constitutively activated orphan GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provide an interesting screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that compound, with an

aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a non-endogenous orphan GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR. Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular

needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12, although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

As noted above, constitutively activated GPCRs that couple to Gi, Gz and Go are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the direct identification of, *e.g*, inverse agonists (which would further decrease this signal), interesting. As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the endogenous GPCR's endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, an endogenous Gi coupled receptor can be fused to a Gs protein – we believe that such a fusion construct, upon expression, "drives" or "forces"

the endogenous GPCR to couple with, *e.g.*, Gs rather than the "natural" Gi protein, such that a cyclase-based assay can be established. Thus, for Gi, Gz and Go coupled receptors, we prefer that that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with Gs (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

Equally effective is a G Protein Fusion construct that utilizes a Gq Protein fused with a Gs, Gi, Gz or Go Protein. A most preferred fusion construct can be accomplished with a Gq Protein wherein the first six (6) amino acids of the G-protein α-subunit ("Gαq") is deleted and the last five (5) amino acids at the C-terminal end of Gαq is replaced with the corresponding amino acids of the Gα of the G protein of interest. For example, a fusion construct can have a Gq (6 amino acid deletion) fused with a Gi Protein, resulting in a "Gq/Gi Fusion Construct". We believe that this fusion construct will force the endogenous Gi coupled receptor to couple to its non-endogenous G protein, Gq, such that the second messenger, for example, inositol triphosphate or diacylgycerol, can be measured in lieu of cAMP production.

4. Co-transfection of a Target Gi Coupled GPCR with a Signal-Enhancer Gs Coupled GPCR (cAMP Based Assays)

A Gi coupled receptor is known to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique in measuring the decrease in production of cAMP as an indication of constitutive activation of a receptor that predominantly couples Gi upon activation can be accomplished by co-transfecting a signal enhancer, *e.g.*, a non-endogenous, constitutively activated receptor that predominantly couples with Gs upon activation (*e.g.*, TSHR-A623I, disclosed below), with the Gi linked GPCR. As is

apparent, constitutive activation of a Gs coupled receptor can be determined based upon an increase in production of cAMP. Constitutive activation of a Gi coupled receptor leads to a decrease in production cAMP. Thus, the co-transfection approach is intended to advantageously exploit these "opposite" affects. For example, co-transfection of a non-endogenous, constitutively activated Gs coupled receptor (the "signal enhancer") with the endogenous Gi coupled receptor (the "target receptor") provides a baseline cAMP signal (*i.e.*, although the Gi coupled receptor will decrease cAMP levels, this "decrease" will be relative to the substantial increase in cAMP levels established by constitutively activated Gs coupled signal enhancer). By then co-transfecting the signal enhancer with a constitutively activated version of the target receptor, cAMP would be expected to further decrease (relative to base line) due to the increased functional activity of the Gi target (*i.e.*, which decreases cAMP).

Screening of candidate compounds using a cAMP based assay can then be accomplished, with two provisos: first, relative to the Gi coupled target receptor, "opposite" effects will result, *i.e.*, an inverse agonist of the Gi coupled target receptor will increase the measured cAMP signal, while an agonist of the Gi coupled target receptor will decrease this signal; second, as would be apparent, candidate compounds that are directly identified using this approach should be assessed independently to ensure that these do not target the signal enhancing receptor (this can be done prior to or after screening against the co-transfected receptors).

F. Medicinal Chemistry

Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having

unique core structures; thereafter, these compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.).

H. Other Utility

Although a preferred use of the non-endogenous versions the human GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists, agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling cascade. The value in non-endogenous human GPCRs is that their utility as a research tool is enhanced in that, because of their unique features, non-endogenous human GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefore is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (*e.g.* from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (*i.e.*, constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure.

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Example 1
ENDOGENOUS HUMAN GPCRS

1. Identification of Human GPCRs

The disclosed endogenous human GPCRs were identified based upon a review of the GenBank™ database information. While searching the database, the following cDNA clones were identified as evidenced below (Table C).

TABLE C

Disclosed Human Orphan GPCRs	Accession Number Identified	Complete DNA Sequence (Base Pairs)	Open Reading Frame (Base Pairs)	Nucleic Acid SEQ.ID. NO.	Amino Acid SEQ.ID. NO.
hRUP8	AL121755	147,566bp	1,152bp	1	2
hRUP9	AC0113375	143,181bp	1,260bp	3	4
hRUP10	AC008745	94,194bp	1,014bp	5	6
hRUP11	AC013396	155,086bp	1,272bp	7	8
hRUP12	AP000808	177,764bp	966bp	9	10
hRUP13	AC011780	167,819bp	1,356bp	11	12
hRUP14	AL137118	168,297bp	1,041bp	13	14
hRUP15	AL016468	138,828bp	1,527bp	15	16
hRUP16	AL136106	208,042bp	1,068bp	17	18
hRUP17	AC023078	161,735bp	969bp	19	20
hRUP18	AC008547	117,304bp	1,305bp	21	22
hRUP19	AC026331	145,183bp	1,041bp	23	24
hRUP20	AL161458	163,511bp	1,011bp	25	26
hRUP21	AC026756	156,534bp	1,014bp	27	28
hRUP22	AC027026	151,811bp	993bp	29	30
hRUP23	AC007104	200,000bp	1,092bp	31	32
hRUP24	AL355388	190,538bp	1,125bp	33	34
hRUP25	AC026331	145,183bp	1,092bp	35	36
hRUP26	AC023040	178,508bp	1,044bp	37	38
hRUP27	AC027643	158,700bp	1,020bp	39	40

2. Full Length Cloning

a. hRUP8 (Seq. Id. Nos. 1 & 2)

The disclosed human RUP8 was identified based upon the use of EST database (*dbEST*) information. While searching the *dbEST*, a cDNA clone with accession number

AL121755 was identified to encode a novel GPCR. The following PCR primers were used for RT-PCR with human testis Marathon-Ready cDNA (Clontech) as templates:

5'-CTTGCAGACATCACCATGGCAGCC-3' (SEQ.ID.NO.:41; sense) and

5'-GTGATGCTCTGAGTACTGGACTGG-3' (SEQ.ID.NO.: 42; antisense).

PCR was performed using Advantage cDNA polymerase (Clontech; manufacturing instructions will be followed) in 50ul reaction by the following cycles: 94°C for 30 sec; 94°C for 10 sec; 65°C for 20 sec, 72°C for 1.5 min, and 72°C for 7 min. Cycles 2 through 4 were repeated 35 times.

A 1.2kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). *See*, SEQ.ID.NO.:1. The putative amino acid sequence for RUP8 is set forth in SEQ.ID.NO.:2.

b. hRUP9 (Seq. Id. Nos. 3 & 4)

The disclosed human RUP9 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC011375 was identified as a human genomic sequence from chromosome 5. The full length RUP9 was cloned by PCR using primers:

5'–GAAGCTGTGAAGAGTGATGC–3' (SEQ.ID.NO.:43; sense),

5'–GTCAGCAATATTGATAAGCAGCAG–3' (SEQ.ID.NO.:44; antisense)

and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) was used for the amplification in a 100μl reaction with 5% DMSO by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 1 minute; 94°C for 30 seconds; 56°C for 30 seconds; 72°C for 2 minutes; 72°C for 5 minutes.

A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) from 1% agarose gel and completely sequenced using the ABI Big Dye

Terminator kit (P.E. Biosystem). *See*, SEQ.ID.NO.:3. The putative amino acid sequence for RUP8 is set forth in SEQ.ID.NO.:4. The sequence of RUP9 clones isolated from human genomic DNA matched with the sequence obtained from data base.

c. hRUP10 (Seq. Id. Nos. 5 & 6)

The disclosed human RUP10 was identified based upon the use of GenBank database information. While searching the database, a cDNA clone with accession number AC008754 was identified as a human genomic sequence from chromosome 19. The full length RUP10 was cloned by RT-PCR using primers:

5'-CCATGGGGAACGATTCTGTCAGCTACG-3' (SEQ.ID.NO.:45; sense) and

5'-GCTATGCCTGAAGCCAGTCTTGTG-3' (SEQ.ID.NO.:46; antisense)

and human leukocyte Marathon-Ready cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50µl reaction by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 30 seconds; 94°C for 10 seconds; 62°C for 20 seconds; 72°C for 1.5 minutes; 72°C for 7 minutes. A 1.0 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). The nucleic acid sequence of the novel human receptor RUP10 is set forth in SEQ.ID.NO.:5 and the putative amino acid sequence thereof is set forth in SEQ.ID.NO.:6.

d. hRUP11 (Seq. Id. Nos. 7 & 8)

The disclosed human RUP11 was identified based upon the use of GenBank database information. While searching the database, a cDNA clone with accession number AC013396 was identified as a human genomic sequence from chromosome 2.

The full length RUP11 was cloned by PCR using primers:

5'-CCAGGATGTTGTGTCACCGTGGTGGC-3' (SEQ.ID.NO.:47; sense),

5'-CACAGCGCTGCAGCCCTGCAGCTGGC-3' (SEQ.ID.NO.:48; antisense)

and human genomic DNA (Clontech) as a template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification in a 50μl reaction by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 minutes; 94°C for 20 seconds; 67°C for 20 seconds; 72°C for 1.5 minutes; 72°C for 7 minutes. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). The nucleic acid sequence of the novel human receptor RUP11 is set forth in SEQ.ID.NO.:7 and the putative amino acid sequence thereof is set forth in SEQ.ID.NO.:8.

e. hRUP12 (Seq. Id. Nos. 9 & 10)

The disclosed human RUP12 was identified based upon the use of GenBank database. While searching the database, a cDNA clone with accession number AP000808 was identified to encode a new GPCR, having significant homology with rat RTA and human mas1 oncogene GPCRs. The full length RUP12 was cloned by PCR using primers:

5'-CTTCCTCTCGTAGGGATGAACCAGAC-3' (SEQ.ID.NO.:49; sense)

5'-CTCGCACAGGTGGGAAGCACCTGTGG-3' (SEQ.ID.NO.:50; antisense)

and human genomic DNA (Clontech) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 min; 94°C for 20 sec; 65°C for 20sec; 72°C for 2 min and 72°C for 7 min. A 1.0kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit

(P.E. Biosystem) (*see,* SEQ.ID.NO.:9 for nucleic acid sequence and SEQ.ID.NO.:10 for deduced amino acid sequence).

f. hRUP13 (Seq. Id. Nos. 11 & 12)

The disclosed human RUP13 was identified based upon the use of GenBank database. While searching the database, a cDNA clone with accession number AC011780 was identified to encode a new GPCR, having significant homology with GPCR fish GPRX-ORYLA. The full length RUP13 was cloned by PCR using primers:

5'-GCCTGTGACAGGAGGTACCCTGG-3' (SEQ.ID.NO.:51; sense)

5'-CATATCCCTCCGAGTGTCCAGCGGC-3' (SEQ.ID.NO.:52; antisense)

and human genomic DNA (Clontech) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to step 4 repeated 35 times: 94°C for 3 min; 94°C for 20 sec; 65°C for 20sec; 72°C for 2 min and 72°C for 7 min. A 1.35kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem) (*see,* SEQ.ID.NO.:11 for nucleic acid sequence and SEQ.ID.NO.:12 for deduced amino acid sequence).

g. hRUP14 (Seq. Id. Nos. 13 & 14)

The disclosed human RUP14 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL137118 was identified as a human genomic sequence from chromosome 13. The full length RUP14 was cloned by PCR using primers:

5'-GCATGGAGAGAAAATTTATGTCCTTGCAACC-3' (SEQ.ID.NO.:53; sense)

5'-CAAGAACAGGTCTCATCTAAGAGCTCC-3' (SEQ.ID.NO.:54; antisense)

and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) and 5% DMSO were used for the amplification by the following cycle

with step 2 and step 3 repeated 35 times: 94°C for 3 minute; 94°C for 20 seconds; 58°C for 2 minutes; 72°C for 10 minutes.

A 1.1 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem) (*see,* SEQ.ID.NO.:13 for nucleic acid sequence and SEQ.ID.NO.:14 for deduced amino acid sequence). The sequence of RUP14 clones isolated from human genomic DNA matched with the sequence obtained from database.

h. hRUP15 (Seq. Id. Nos. 15 & 16)

The disclosed human RUP15 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC016468 was identified as a human genomic sequence. The full length RUP15 was cloned by PCR using primers:

5'-GCTGTTGCCATGACGTCCACCTGCAC-3' (SEQ.ID.NO.:55; sense)

5'-GGACAGTTCAAGGTTTGCCTTAGAAC-3' (SEQ.ID.NO.:56; antisense)

and human genomic DNA (Promega) as a template. Taq Plus Precision polymerase (Stratagene) was used for the amplification by the following cycle with step 2 to 4 repeated 35 times: 94°C for 3 minute; 94°C for 20 seconds; 65°C for 20 seconds; 72°C for 2 minutes and 72°C for 7 minutes.

A 1.5 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). *See*, SEQ.ID.NO.:15 for nucleic acid sequence and SEQ.ID.NO.:16 for deduced amino acid sequence. The sequence of RUP15 clones isolated from human genomic DNA matched with the sequence obtained from database.

i. hRUP16 (Seq. Id. Nos. 17 & 18)

The disclosed human RUP16 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL136106 was identified as a human genomic sequence from chromosome 13. The full length RUP16 was cloned by PCR using primers:

5'-CTTTCGATACTGCTCCTATGCTC-3' (SEQ.ID.NO.:57; sense, 5' of initiation codon),

5'-GTAGTCCACTGAAAGTCCAGTGATCC-3' (SEQ.ID.NO.:58; antisense, 3' of stop codon)

and human skeletal muscle Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 to 4 repeated 35 times: 94°C for 30 seconds; 94°C for 5 seconds; 69°C for 15 seconds; 72°C for 1 minute and 72°C for 5 minutes.

A 1.1 Kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the T7 sequenase kit (Amsham). *See*, SEQ.ID.NO.:17 for nucleic acid sequence and SEQ.ID.NO.:18 for deduced amino acid sequence. The sequence of RUP16 clones matched with four unordered segments of AL136106, indicating that the RUP16 cDNA is composed of 4 exons.

j. hRUP17 (Seq. Id. Nos. 19 & 20)

The disclosed human RUP17 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC023078 was identified as a human genomic sequence from chromosome 11. The full length RUP17 was cloned by PCR using primers:

5'-TTTCTGAGCATGGATCCAACCATCTC-3' (SEQ.ID.NO.:59; sense, containing initiation codon)

5'-CTGTCTGACAGGGCAGAGGCTCTTC-3' (SEQ.ID.NO.:60; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification in a 100ul reaction with 5% DMSO by the

following cycle with step 2 to 4 repeated 30 times: 94°C for 1 min; 94°C for 15 sec; 67°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 970bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:19 for nucleic acid sequence and SEQ.ID.NO.:20 for deduced amino acid sequence.

k. hRUP18 (Seq. Id. Nos. 21 & 22)

The disclosed human RUP18 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC008547 was identified as a human genomic sequence from chromosome 5. The full length RUP18 was cloned by PCR using primers:

5'-GGAACTCGTATAGACCCAGCGTCGCTCC-3' (SEQ.ID.NO.:61; sense, 5' of the initiation codon),

5'-GGAGGTTGCGCCTTAGCGACAGATGACC-3' (SEQ.ID.NO.:62; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. TaqPlus precision DNA polymerase (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 95°C for 5 min; 95°C for 30 sec; 65°C for 30 sec; 72°C for 2 min; and 72°C for 5 min.

A 1.3kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:21 for nucleic acid sequence and SEQ.ID.NO.:22 for deduced amino acid sequence.

l. hRUP19 (Seq. Id. Nos. 23 & 24)

The disclosed human RUP19 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length RUP19 was cloned by PCR using primers:

5'-CTGCACCCGGACACTTGCTCTG-3' (SEQ.ID.NO.:63; sense, 5' of initiation codon),

5'-GTCTGCTTGTTCAGTGCCACTCAAC-3' (SEQ.ID.NO.:64; antisense, containing the stop codon)

and human genomic DNA (Promega) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 min; 94°C for 15 sec; 70°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 1.1kp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:23 for nucleic acid sequence and SEQ.ID.NO.:24 for deduced amino acid sequence.

m. hRUP20 (Seq. Id. Nos. 25 & 26)

The disclosed human RUP20 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AL161458 was identified as a human genomic sequence from chromosome 1. The full length RUP20 was cloned by PCR using primers:

5'-TATCTGCAATTCTATTCTAGCTCCTG-3' (SEQ.ID.NO.:65; sense, 5' of initiation codon),

5'-TGTCCCTAATAAAGTCACATGAATGC-3' (SEQ.ID.NO.:66; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clonetech) was used for the amplification with 5% DMSO by the following cycle with

step 2 to 4 repeated 35 times: 94°C for 1 min; 94°C for 15 sec; 60°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 1.0 kp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:25 for nucleic acid sequence and SEQ.ID.NO.:26 for deduced amino acid sequence.

n. hRUP21 (Seq. Id. Nos. 27 & 28)

The disclosed human RUP21 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC026756 was identified as a human genomic sequence from chromosome 13. The full length RUP21 was cloned by PCR using primers:

5'– GGAGACAACCATGAATGAGCCAC –3' (SEQ.ID.NO.:67; sense)

5'– TATTTCAAGGGTTGTTTGAGTAAC –3' (SEQ.ID.NO.:68; antisense)

and human genomic DNA (Promega) as template. Taq Plus Precision polymerase (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 30 times: 94°C for 1 min; 94°C for 15 sec; 55°C for 20 sec; 72°C for 1 min and 30 sec; and 72°C for 5 min.

A 1,014 bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:27 for nucleic acid sequence and SEQ.ID.NO.:28 for deduced amino acid sequence.

o. hRUP22 (Seq. Id. Nos. 29 & 30)

The disclosed human RUP22 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession

Number AC027026 was identified as a human genomic sequence from chromosome 11. The full length RUP22 was cloned by PCR using primers:

5'– GGCACCAGTGGAGGTTTTCTGAGCATG –3' (SEQ.ID.NO.:69; sense, containing initiation codon)

5'-CTGATGGAAGTAGAGGCTGTCCATCTC-3' (SEQ.ID.NO.:70; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. TaqPlus Precision DNA polymerase (Stratagene) was used for the amplification in a 100ul reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 30 times: 94°C, 1 minutes 94°C, 15 seconds 55°C, 20 seconds 72°C, 1.5 minute 72°C, 5 minutes.

A 970bp PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:29 for nucleic acid sequence and SEQ.ID.NO.:30 for deduced amino acid sequence.

p. hRUP23 (Seq. Id. Nos. 31 & 32)

The disclosed human RUP23 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC007104 was identified as a human genomic sequence from chromosome 4. The full length RUP23 was cloned by PCR using primers:

5'-CCTGGCGAGCCGCTAGCGCCATG-3' (SEQ.ID.NO.:71; sense, ATG as the initiation codon),

5'-ATGAGCCCTGCCAGGCCCTCAGT-3' (SEQ.ID.NO.:72; antisense, TCA as the stop codon)

and human placenta Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following

cycle with step 2 to 4 repeated 35 times: 95°C for 30 sec; 95°C for 15 sec; 66°C for 20 sec; 72°C for 1 min and 20 sec; and 72°C for 5 min.

A 1.0 kb PCR fragment was isolated and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:31 for nucleic acid sequence and SEQ.ID.NO.:32 for deduced amino acid sequence.

q. hRUP24 (Seq. Id. Nos. 33 & 34)

The disclosed human RUP25 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length RUP25 was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:73; sense, 5'of initiation codon),

5'-AGATCCTGGTTCTTGGTGACAATG-3' (SEQ.ID.NO.:74; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:33 for nucleic acid sequence and SEQ.ID.NO.:34 for deduced amino acid sequence.

r. hRUP25 (Seq. Id. Nos. 35 & 36)

The disclosed human RUP25 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession

Number AC026331 was identified as a human genomic sequence from chromosome 12. The full length RUP25 was cloned by PCR using primers:

5'-GCTGGAGCATTCACTAGGCGAG-3' (SEQ.ID.NO.:75; sense, 5'of initiation codon),

5'-AGATCCTGGTTCTTGGTGACAATG-3' (SEQ.ID.NO.:76; antisense, 3' of stop codon)

and human genomic DNA (Promega) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 15 seconds; 56°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.2kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:35 for nucleic acid sequence and SEQ.ID.NO.:36 for deduced amino acid sequence.

s. hRUP26 (Seq. Id. Nos. 37 & 38)

The disclosed human RUP26 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC023040 was identified as a human genomic sequence from chromosome 2. The full length RUP26 was cloned by RT-PCR using RUP26 specific primers:

5'-AGCCATCCCTGCCAGGAAGC<u>ATG</u>G-3' (SEQ.ID.NO.:77; sense, containing initiation codon)

5'-CCAGACTGTGGACTCAAGAACT<u>CTA</u>GG-3' (SEQ.ID.NO.:78; antisense, containing stop codon)

and human pancreas Marathon - Ready cDNA (Clontech) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification in a 100µl reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 5 minute; 95°C for 30 seconds; 65°C for 30 seconds 72°C for 2 minute and 72°C for 5 minutes.

A 1.1kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:37 for nucleic acid sequence and SEQ.ID.NO.:38 for deduced amino acid sequence.

t. hRUP27 (Seq. Id. Nos. 39 & 40)

The disclosed human RUP27 was identified based upon the use of GeneBank database information. While searching the database, a cDNA clone with Accession Number AC027643 was identified as a human genomic sequence from chromosome 12. The full length RUP27 was cloned by PCR using RUP27 specific primers:

5'-AGTCCACGAACAATGAATCCATTTCATG-3' (SEQ.ID.NO.:79; sense, containing initiation codon),

5'-ATCATGTCTAGACTCATGGTGATCC-3' (SEQ.ID.NO.:80; antisense, 3' of stop codon) and the human adult brain Marathon-Ready cDNA (Clontech) as template. Advantage cDNA polymerase mix (Clontech) was used for the amplification in a 50μl reaction with 5% DMSO by the following cycle with step 2 to 4 repeated 35 times: 94°C for 1 minute; 94°C for 10 seconds; 58°C for 20 seconds 72°C for 1 minute 30 seconds and 72°C for 5 minutes.

A 1.1kb PCR fragment was isolated from 1% agarose gel and cloned into the pCRII-TOPO vector (Invitrogen) and completely sequenced using the ABI Big Dye Termiantor Kit (P.E. Biosystem). *See*, SEQ.ID.NO.:35 for nucleic acid sequence and SEQ.ID.NO.:36 for deduced amino acid sequence. The sequence of RUP27 cDNA clone isolated from human brain was determined to match with five unordered segments of AC027643, indicating that the RUP27 cDNA is composed of 5 exons.

Example 2
PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS

Those skilled in the art are credited with the ability to select techniques for mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16^{th} amino acid (located in the IC3 region of the GPCR) from a conserved proline (or an endogenous, conservative substitution therefore) residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, preferably to an alanine, histidine, arginine or lysine amino acid residue, most preferably to a lysine amino acid residue.

1. Transformer Site-Directed ™ Mutagenesis

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table D):

TABLE D

Receptor Identifier	Codon Mutation
hRUP8	V274K
hRUP9	T249K
hRUP10	R232K
hRUP11	M294K
hRUP12	F220K
hRUP16	A238K

hRUP17	Y215K
hRUP18	L294K
hRUP19	T219K
hRUP20	K248A K248H K248R
hRUP21	R240K
hRUP22	Y222K
hRUP24	A245K
hRUP25	I230K
hRUP26	V285K
hRUP27	T248K

2. QuikChange™ Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs can also be accomplished by using QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (included in kit). For convenience, the codon mutation incorporated into the novel human GPCR and the respective oligonucleotides are noted, in standard form (Table E):

TABLE E

Receptor Identifier	Codon Mutation	5'-3' orientation (sense), (SEQ.ID.NO.) mutation underlined	5'-3' orientation (antisense) (SEQ.ID.NO.)	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 16 times
hRUP13	A268K	GGGGAGGGAAAGCAA AGGTGGTCCTCCTGG (81)	CCAGGAGAACCACCT TTGCTTTCCCTCCCC (82)	98° for 2' 98° for 30" 56°C for 30" 72° for 11' 40" 72° for 5'
hRUP14	L246K	CAGGAAGGCAAAGAC CACCATCATCATC (85)	GATGATGATGGTGGT CTTTGCCTTCCTG (86)	98° for 2' 98° for 30" 55°C for 30" 72° for 11' 40" 72° for 5'

hRUP15	A398K	CCAGTGCAAAGCTAAG AAAGTGATCTTC (89)	GAAGATCACTTTCTTA GCTTTGCACTGG (90)	98° for 2' 98° for 30" 55°C for 30" 72° for 11' 40" 72° for 5'
hRUP23	W275K	GCCGCCACCGCGCCAA GAGGAAGATTGGC (93)	GCCAATCTTCCTCTTG GCGCGGTGGCGGC (94)	98° for 2' 98° for 30" 56°C for 30" 72° for 11' 40" 72° for 5'

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table F below:

TABLE F

Non Endogenous Human GPCR	Nucleic Acid Sequence Listing	Amino Acid Sequence Listing
hRUP13	SEQ.ID.NO.:83	SEQ.ID.NO.:84
hRUP14	SEQ.ID.NO.:87	SEQ.ID.NO.:88
hRUP15	SEQ.ID.NO.:91	SEQ.ID.NO.:92
hRUP23	SEQ.ID.NO.:95	SEQ.ID.NO.:96

Example 3
RECEPTOR EXPRESSION

Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretary pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of

potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

a. Transient Transfection

On day one, $6x10^6$/ 10 cm dish of 293 cells well were plated out. On day two, two reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 4μg DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 0.5 ml serum free DMEM (Gibco BRL); tube B was prepared by mixing 24μl lipofectamine (Gibco BRL) in 0.5ml serum free DMEM. Tubes A and B were admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells were washed with 1XPBS, followed by addition of 5 ml serum free DMEM. 1 ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture was removed by aspiration, followed by the addition of 10ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO_2. After 48hr incubation, cells were harvested and utilized for analysis.

b. Stable Cell Lines: Gs Fusion Protein

Approximately $12x10^6$ 293 cells are plated on a 15cm tissue culture plate. Grown in DME High Glucose Medium containing ten percent fetal bovine serum and one percent sodium pyruvate, L-glutamine, and anti-biotics. Twenty-four hours following plating of 293 cells to ~80% confluency, the cells are transfected using 12μg of DNA. The 12μg of DNA is combined with 60ul of lipofectamine and 2mL of DME High Glucose Medium without serum. The medium is aspirated from the plates and the cells are washed once with medium without serum. The DNA, lipofectamine, and

medium mixture is added to the plate along with 10mL of medium without serum. Following incubation at 37 degrees Celsius for four to five hours, the medium is aspirated and 25ml of medium containing serum is added. Twenty-four hours following transfection, the medium is aspirated again, and fresh medium with serum is added. Forty-eight hours following transfection, the medium is aspirated and medium with serum is added containing geneticin (G418 drug) at a final concentration of 500μg/mL. The transfected cells now undergo selection for positively transfected cells containing the G418 resistant gene. The medium is replaced every four to five days as selection occurs. During selection, cells are grown to create stable pools, or split for stable clonal selection.

Example 4
ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane Binding Assays: [^{35}S]GTPγS Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [^{35}S]GTPγS, can be utilized to demonstrate enhanced binding of [^{35}S]GTPγS to membranes expressing constitutively activated receptors. The advantage of using

[^{35}S]GTPγS binding to measure constitutive activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [^{35}S]GTPγS binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [^{35}S]GTPγS assay was incubated in 20 mM HEPES and between 1 and about 20mM $MgCl_2$ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [^{35}S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane protein (*e.g*, 293 cells expressing the Gs Fusion Protein; this amount can be adjusted for optimization) and 10 μM GDP (this amount can be changed for optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) were then added and the mixture incubated for another 30 minutes at room temperature. The tubes were then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

2. Adenylyl Cyclase

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells can contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP

antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells were harvested approximately twenty four hours after transient transfection. Media is carefully aspirated off and discarded. 10ml of PBS is gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS are added to each plate. Cells were pipeted off the plate and the cell suspension was collected into a 50ml conical centrifuge tube. Cells were then centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet was carefully re-suspended into an appropriate volume of PBS (about 3ml/plate). The cells were then counted using a hemocytometer and additional PBS was added to give the appropriate number of cells (with a final volume of about 50 µl/well).

cAMP standards and Detection Buffer (comprising 1 µCi of tracer [^{125}I cAMP (50 µl] to 11 ml Detection Buffer) was prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 50µl of Stimulation Buffer, 3ul of test compound (12uM final assay concentration) and 50µl cells, Assay Buffer was stored on ice until utilized. The assay was initiated by addition of 50µl of cAMP standards to appropriate wells followed by addition of 50ul of PBSA to wells H-11 and H12. 50µl of Stimulation Buffer was added to all wells. DMSO (or selected candidate compounds) was added to appropriate wells using a pin tool capable of dispensing 3µl of compound solution, with a final assay concentration of 12µM test compound and 100µl total assay volume. The cells were then added to the wells and incubated for 60 min at room temperature. 100µl of Detection Mix containing tracer cAMP was then added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation

counter. Values of cAMP/well were then extrapolated from a standard cAMP curve which was contained within each assay plate.

3. Cell-Based cAMP for Gi Coupled Target GPCRs

TSHR is a Gs coupled GPCR that causes the accumulation of cAMP upon activation. TSHR will be constitutively activated by mutating amino acid residue 623 (*i.e.*, changing an alanine residue to an isoleucine residue). A Gi coupled receptor is expected to inhibit adenylyl cyclase, and, therefore, decrease the level of cAMP production, which can make assessment of cAMP levels challenging. An effective technique for measuring the decrease in production of cAMP as an indication of constitutive activation of a Gi coupled receptor can be accomplished by co-transfecting, most preferably, non-endogenous, constitutively activated TSHR (TSHR-A623I) (or an endogenous, constitutively active Gs coupled receptor) as a "signal enhancer" with a Gi linked target GPCR to establish a baseline level of cAMP. Upon creating a non-endogenous version of the Gi coupled receptor, this non-endogenous version of the target GPCR is then co-transfected with the signal enhancer, and it is this material that can be used for screening. We will utilize such approach to effectively generate a signal when a cAMP assay is used; this approach is preferably used in the direct identification of candidate compounds against Gi coupled receptors. It is noted that for a Gi coupled GPCR, when this approach is used, an inverse agonist of the target GPCR will increase the cAMP signal and an agonist will decrease the cAMP signal.

On day one, $2X10^4$ 293 and 293 cells/well will be plated out. On day two, two reaction tubes will be prepared (the proportions to follow for each tube are per plate): tube A will be prepared by mixing 2μg DNA of each receptor transfected into the mammalian cells, for a total of 4μg DNA (*e.g.*, pCMV vector; pCMV vector with mutated THSR (TSHR-A623I); TSHR-A623I and GPCR, etc.) in 1.2ml serum free

DMEM (Irvine Scientific, Irvine, CA); tube B will be prepared by mixing 120µl lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B will then be admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture". Plated 293 cells will be washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture will then be added to the cells, followed by incubation for 4hrs at 37°C/5% CO_2. The transfection mixture will then be removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells will then be incubated at 37°C/5% CO_2. After 24hr incubation, cells will then be harvested and utilized for analysis.

A Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is designed for cell-based assays, however, can be modified for use with crude plasma membranes depending on the need of the skilled artisan. The Flash Plate wells will contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells can be quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in whole cells that express the receptors.

Transfected cells will be harvested approximately twenty four hours after transient transfection. Media will be carefully aspirated off and discarded. 10ml of PBS will be gently added to each dish of cells followed by careful aspiration. 1ml of Sigma cell dissociation buffer and 3ml of PBS will be added to each plate. Cells will be pipeted off the plate and the cell suspension will be collected into a 50ml conical centrifuge tube. Cells will then be centrifuged at room temperature at 1,100 rpm for 5 min. The cell pellet will be carefully re-suspended into an appropriate volume of PBS (about

3ml/plate). The cells will then be counted using a hemocytometer and additional PBS is added to give the appropriate number of cells (with a final volume of about 50μl/well).

cAMP standards and Detection Buffer (comprising 1 μCi of tracer [^{125}I cAMP (50 μl] to 11 ml Detection Buffer) will be prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer should be prepared fresh for screening and contained 50μl of Stimulation Buffer, 3ul of test compound (12uM final assay concentration) and 50μl cells, Assay Buffer can be stored on ice until utilized. The assay can be initiated by addition of 50μl of cAMP standards to appropriate wells followed by addition of 50μl of PBSA to wells H-11 and H12. 50ul of Stimulation Buffer will be added to all wells. Selected compounds (*e.g.*, TSH) will be added to appropriate wells using a pin tool capable of dispensing 3μl of compound solution, with a final assay concentration of 12μM test compound and 100μl total assay volume. The cells will then be added to the wells and incubated for 60 min at room temperature. 100μl of Detection Mix containing tracer cAMP will then be added to the wells. Plates were then incubated additional 2 hours followed by counting in a Wallac MicroBeta scintillation counter. Values of cAMP/well will then be extrapolated from a standard cAMP curve which is contained within each assay plate.

4. Reporter-Based Assays

a. CRE-LUC Reporter Assay (Gs-associated receptors)

293 and 293T cells are plated-out on 96 well plates at a density of 2 x 10^4 cells per well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture is prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100μl of DMEM were gently mixed with 2μl of lipid in 100μl of DMEM (the 260ng of plasmid DNA consisted of

200ng of a 8xCRE-Luc reporter plasmid, 50ng of pCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8XCRE-Luc reporter plasmid was prepared as follows: vector SRIF-β-gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the pβgal-Basic Vector (Clontech). Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (*see*, 7 *Human Gene Therapy* 1883 (1996)) and cloned into the SRIF-β-gal vector at the Kpn-BglV site, resulting in the 8xCRE-β-gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE-β-gal reporter vector with the luciferase gene obtained from the pGL3-basic vector (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture was diluted with 400 µl of DMEM and 100µl of the diluted mixture was added to each well. 100 µl of DMEM with 10% FCS were added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells were changed with 200 µl/well of DMEM with 10% FCS. Eight (8) hours later, the wells were changed to 100 µl /well of DMEM without phenol red, after one wash with PBS. Luciferase activity were measured the next day using the LucLite™ reporter gene assay kit (Packard) following manufacturer instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

b. AP1 reporter assay (Gq-associated receptors)

A method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A Pathdetect™ AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) can be utilized following the protocol set forth above with respect to the

CREB reporter assay, except that the components of the calcium phosphate precipitate were 410 ng pAP1-Luc, 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP.

c. SRF-LUC Reporter Assay (Gq- associated receptors)

One method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A Pathdetect™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay for Gq coupled activity in, *e.g.*, COS7 cells. Cells are transfected with the plasmid components of the system and the indicated expression plasmid encoding endogenous or non-endogenous GPCR using a Mammalian Transfection™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1μM Angiotensin, where indicated. Cells are then lysed and assayed for luciferase activity using a Luclite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data can be analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

d. Intracellular IP_3 Accumulation Assay (Gq-associated receptors)

On day 1, cells comprising the receptors (endogenous and/or non-endogenous) can be plated onto 24 well plates, usually $1x10^5$ cells/well (although his umber can be optimized. On day 2 cells can be transfected by firstly mixing 0.25µg DNA in 50 µl serum free DMEM/well and 2 µl lipofectamine in 50 µl serumfree DMEM/well. The solutions are gently mixed and incubated for 15-30 min at room temperature. Cells are washed with 0.5 ml PBS and 400 µl of serum free media is mixed with the transfection media and added to the cells. The cells are then incubated for 3-4 hrs at 37°C/5%CO_2 and then the transfection media is removed and replaced with 1ml/well of regular growth media. On day 3 the cells are labeled with ^{3}H-myo-inositol. Briefly, the media is removed and the cells are washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum free media (GIBCO BRL) is added/well with 0.25 µCi of ^{3}H-myo-inositol/ well and the cells are incubated for 16-18 hrs o/n at 37°C/5%CO_2. On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium is added containing inositol-free/serum free media 10 µM pargyline 10 mM lithium chloride or 0.4 ml of assay medium and 50µl of 10x ketanserin (ket) to final concentration of 10µM. The cells are then incubated for 30 min at 37°C. The cells are then washed with 0.5 ml PBSand 200µl of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added/well. The solution is kept on ice for 5-10 min or until cells were lysed and then neutralized by 200 µl of fresh/ice cold neutralization sol. (7.5 % HCL). The lysate is then transferred into 1.5 ml eppendorf tubes and 1 ml of chloroform/methanol (1:2) is added/tube. The solution is vortexed for 15 sec and the upper phase is applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). Firstly, the resin is washed with water at 1:1.25 W/V and 0.9 ml of upper phase is loaded onto the column. The column is washed with 10 mls of 5 mM myo-inositol and 10 ml of 5 mM Na-borate/60mM Na-formate. The inositol

tris phosphates are eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns are regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H_2O and stored at 4°C in water.

Exemplary results are presented below in Table G:

TABLE G

Receptor	Mutation	Assay Utilized Figure No.)	Signal Generated: CMV	Signal Generated: Endogenous Version (Relative Light Units)	Signal Generated: Non-Endogenous Version (Relative Light Units)	Difference (⇐⟨) Between . CMV v. Wild-type . Wild-type v. Mutant
hRUP12	N/A	IP_3 (Figure 1)	317.03 cpm/mg protein	3463.29 cpm/mg protein	--	1. 11 Fold ⇐
hRUP13	N/A	cAMP (Figure 2)	8.06 pmol/cAMP/mg protein	19.10 pmol/cAMP/mg protein	--	1. 2.4 Fold ⇐
	A268K	8XCRE-LUC (Figure 3)	3665.43 LCPS	83280.17 LPCS	61713.6 LCPS	1. 23 Fold ⇐ 2. 26 % ⟨
hRUP14	L246K	8XCRE-LUC (Figure 5)	86.07 LCPS	1962.87 LCPS	789.73 LCPS	1. 23 Fold ⇐ 2. 60% ⟨
hRUP15	A398K	8XCRE-LUC (Figure 6)	86.07 LCPS	18286.77 LCPS	17034.83 LCPS	1. 212 Fold ⇐ 2. 1% ⟨
	A398K	cAMP (Figure 7)	15.00 pmol/cAMP/mg protein	164.4 pmol/cAMP/mg protein	117.5 pmol/cAMP/ mg protein	1. 11 Fold ⇐ 2. 29% ⟨
hRUP17	N/A	IP_3 (Figure 9)	317.03 cpm/mg protein	741.07 cpm/mg protein	--	1. 2.3 Fold ⇐
hRUP21	N/A	IP_3 (Figure 10)	730.5 cpm/mg protein	1421.9 cpm/mg protein	--	1. 2 Fold ⇐
hRUP23	W275K	8XCRE-LUC (Figure 11)	311.73 pmol/cAMP/mg protein	13756.00 pmol/cAMP/mg protein	9756.87 pmol/cAMP/ mg protein	1. 44 Fold ⇐ 2. 30% ⟨

N/A = not applied

Exemplary results of GTPγS assay for detecting constitutive activation, as disclosed in Example 4(1) above, was accomplished utilizing Gs:Fusion Protein Constructs on human RUP13 and RUP15. Table H below lists the signals generated from this assay and the difference in signals as indicated:

TABLE H

Receptor: Gs Fusion Protein	Assay Utilized	Signal Generated: CMV (cpm bound GTP)	Signal Generated: Fusion Protein (cpm bound GTP)	Signal Generated: CMV+ 10μMGDP (cpm bound GTP)	Signal Generated: Fusion Protein + 10μM GDP (cpm bound GTP)	Difference Between: 1. CMV v. Fusion Protein 2. CMV+GDP vs. Fusion+GDP 3. Fusion vs. Fusion+GDP (cpm bound GTP)
hRUP13-Gs	GTPγS (Figure 4)	32494.0	49351.30	11148.30	28834.67	1. 1.5 Fold ⇐ 2. 2.6 Fold ⇐ 3. 42% ⟨
hRUP15-Gs	GTPγS (Figure 8)	30131.67	32493.67	7697.00	14157.33	1. 1.1 Fold ⇐ 2. 1.8 Fold ⇐ 3. 56% ⟨

Example 5
FUSION PROTEIN PREPARATION

a. GPCR:Gs Fusion Constuct

The design of the constitutively activated GPCR-G protein fusion construct was accomplished as follows: both the 5' and 3' ends of the rat G protein Gsα (long form; Itoh, H. et al., 83 *PNAS* 3776 (1986)) were engineered to include a HindIII (5'-AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence was shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct orientation for the Gsα sequence was determined after

subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat Gsα gene at HindIII sequence was then verified; this vector was now available as a "universal" Gsα protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus beneficially providing the ability to insert, upstream of the Gs protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other "universal" G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized – the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

RUP13 couples via Gs. For the following exemplary GPCR Fusion Proteins, fusion to Gsα was accomplished.

A RUP13-Gsα Fusion Protein construct was made as follows: primers were designed as follows:

5'-gatc[TCTAGAAT]GGAGTCCTCACCCATCCCCCAG -3' (SEQ.ID.NO.:97; sense)

5'-gatc[GATATC]CGTGACTCCAGCCGGGGTGAGGCGGC-3' (SEQ.ID.NO.:98; antisense).

Nucleotides in lower caps are included as spacers in the restriction sites (designated in brackets) between the G protein and RUP13. The sense and anti-sense primers included the restriction sites for XbaI and EcoRV, respectively, such that spacers (attributed to the restriction sites) exists between the G protein and RUP15.

PCR was then utilized to secure the respective receptor sequences for fusion within the Gsα universal vector disclosed above, using the following protocol for each: 100ng cDNA for RUP15 was added to separate tubes containing 2μl of each primer (sense and anti-sense), 3μL of 10mM dNTPs, 10μL of 10XTaqPlus™ Precision buffer, 1μL of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80μL of water. Reaction temperatures and cycle times for RUP15 were as follows with cycle steps 2

through 4 were repeated 35 times: 94°C for 1 min; 94°C for 30 seconds; 62°C for 20 sec; 72°C 1 min 40sec; and 72° C 5 min . PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested with XbaI and EcoRV and the desired inserts purified and ligated into the Gs universal vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for RUP15-Gs Fusion Protein was sequenced to verify correctness. (See, SEQ.ID.NO.:99 for nucleic acid sequence and SEQ.ID.NO.:100 for amino acid sequence).

RUP15 couples via Gs. For the following exemplary GPCR Fusion Proteins, fusion to Gsα was accomplished.

A RUP15-Gsα Fusion Protein construct was made as follows: primers were designed as follows:

5'-TCTAGAATGACGTCCACCTGCACCAACAGC-3' (SEQ.ID.NO.:101; sense)

5'-gatatcGCAGGAAAAGTAGCAGAATCGTAGGAAG-3' (SEQ.ID.NO.:102; antisense).

Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and RUP15. The sense and anti-sense primers included the restriction sites for EcoRV and Xba1, respectively, such that spacers (attributed to the restriction sites) exists between the G protein and RUP15.

PCR was then utilized to secure the respective receptor sequences for fusion within the Gsα universal vector disclosed above, using the following protocol for each: 100ng cDNA for RUP15 was added to separate tubes containing 2μl of each primer (sense and anti-sense), 3μL of 10mM dNTPs, 10μL of 10XTaqPlus™ Precision buffer, 1uL of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80μL of water. Reaction temperatures and cycle times for RUP15 were as follows with cycle steps 2

through 4 were repeated 35 times: 94°C for 1 min; 94°C for 30 seconds; 62°C for 20 sec; 72°C 1 min 40sec; and 72° C 5 min . PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested). The purified product was digested with EcoRV and Xba1 and the desired inserts purified and ligated into the Gs universal vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for RUP15-Gs Fusion Protein was sequenced to verify correctness. (See, SEQ.ID.NO.:103 for nucleic acid sequence and SEQ.ID.NO.:104 for amino acid sequence).

b. Gq(6 amino acid deletion)/Gi Fusion Construct

The design of a Gq (del)/Gi fusion construct can be accomplished as follows: the N-terminal six (6) amino acids (amino acids 2 through 7, having the sequence of TLESIM (SEQ.ID.NO.: 129) Gαq-subunit will be deleted and the C-terminal five (5) amino acids, having the sequence EYNLV (SEQ.ID.NO.:130) will be replace with the corresponding amino acids of the Gαi Protein, having the sequence DCGLF (SEQ.ID.NO.:131). This fusion construct will be obtained by PCR using the following primers:

5'-gatcaagcttcCATGGCGTGCTGCCTGAGCGAGGAG-3' (SEQ.ID.NO.:132) and

5'-gatcggatccTTAGAACAGGCCGCAGTCCTTCAGGTTCAGCTGCAGGATGGTG-3' (SEQ.ID.NO.:133)

and Plasmid 63313 which contains the mouse Gαq-wild type version with a hemagglutinin tag as template. Nucleotides in lower caps are included as spacers.

TaqPlus Precision DNA polymerase (Stratagene) will be utilized for the amplification by the following cycles, with steps 2 through 4 repeated 35 times: 95°C

for 2 min; 95°C for 20 sec; 56°C for 20 sec; 72°C for 2 min; and 72°C for 7 min. The PCR product will be cloned into a pCRII-TOPO vector (Invitrogen) and sequenced using the ABI Big Dye Terminator kit (P.E. Biosystem). Inserts from a TOPO clone containing the sequence of the fusion construct will be shuttled into the expression vector pcDNA3.1(+) at the HindIII/BamHI site by a 2 step cloning process.

Example 6
TISSUE DISTRIBUTION OF THE DISCLOSED HUMAN GPCRs: RT-PCR

RT-PCR was applied to confirm the expression and to determine the tissue distribution of several novel human GPCRs. Oligonucleotides utilized were GPCR-specific and the human multiple tissue cDNA panels (MTC, Clontech) as templates. Taq DNA polymerase (Stratagene) were utilized for the amplification in a 40µl reaction according to the manufacturer's instructions. 20µl of the reaction will be loaded on a 1.5% agarose gel to analyze the RT-PCR products. Table J below lists the receptors, the cycle conditions and the primers utizilized.

TABLE J

Receptor Identifier	Cycle Conditions Min ('), Sec (") Cycles 2-4 repeated 30 times	5' Primer (SEQ.ID.NO.)	3' Primer (SEQ.ID.NO.)	DNA Fragment	Tissue Expression
hRUP10	94° for 30" 94° for 10" 62°C for 20" 72° for 1' 72° for 7' *cycles 2-4 repeated 35 times	CATGTATGC CAGCGTCCT GCTCC (105)	GCTATGCCTG AAGCCAGTC TTGTG (106)	730bp	Kidney, leukocyte, liver, placenta and spleen
hRUP11	94° for 2' 94° for 15" 67°C for 15" 72° for 45" 72° for 5'	GCACCTGCT CCTGAGCAC CTTCTCC (107)	CACAGCGCT GCAGCCCTG CAGCTGGC (108)	630bp	Liver, kidney, pancreas, colon, small intestinal, spleen and prostate

hRUP12	94° for 2' 94° for 15" 66°C for 15" 72° for 45" 72° for 5'	CCAGTGATG ACTCTGTCC AGCCTG (109)	CAGACACTT GGCAGGGAC GAGGTG (110)	490bp	Brain, colon, heart, kidney, leukocyte, pancreas, prostate, small intestinal, spleen, testis, and thymus

hRUP13	94° for 1' 94° for 15" 68°C for 20" 72° for 1' 45" 72° for 5'	CTTGTGGTCT ACTGCAGCA TGTTCCG (111)	CATATCCCTC CGAGTGTCC AGCGGC (112)	700bp	Placenta and lung
hRUP14	94° for 1' 94° for 15" 68°C for 20" 72° for 1' 45" 72° for 5'	ATGGATCCT TATCATGGC TTCCTC (113)	CAAGAACAG GTCTCATCTA AGAGCTCC (114)	700bp	Not yet determined
hRUP16	94° for 30" 94° for 5" 69°C for 15" 72° for 30" 72° for 5'	CTCTGATGC CATCTGCTG GATTCCTG (115)	GTAGTCCACT GAAAGTCCA GTGATCC (116)	370bp	Fetal brain, fetal kidney and fetal skeletal muscle
hRUP18	94° for 2' 94° for 15" 60°C for 20" 72° for 1' 72° for 5'	TGGTGGCGA TGGCCAACA GCGCTC (117)	GTTGCGCCTT AGCGACAGA TGACC (118)	330bp	Pancreas
hRUP21	94° for 1' 94° for 15" 56°C for 20" 72° for 40" *cycles 2-3 repeated 30 times	TCAACCTGT ATAGCAGCA TCCTC (119)	AAGGAGTAG CAGAATGGT TAGCC (120)		Kidney, lung and testis
hRUP22	94° for 30" 94° for 15" 69°C for 20" 72° for 40" *cycles 2-3 repeated 30 times	GACACCTGT CAGCGGTCG TGTGTG (121)	CTGATGGAA GTAGAGGCT GTCCATCTC (122)		Testis, thymus and spleen
hRUP23	94° for 2' 94° for 15" 60°C for 20" 72° for 1' 72° for 5'	GCGCTGAGC GCAGACCAG TGGCTG (123)	CACGGTGAC GAAGGGCAC GAGCTC (124)	520bp	Placenta
hRUP26	94° for 2' 94° for 15" 65°C for 20" 72° for 1' 72° for 5'	AGCCATCCC TGCCAGGAA GCATGG (125)	CCAGGTAGG TGTGCAGCA CAATGGC (126)	470bp	Pancreas
hRUP27	94° for 30" 94° for 10" 55°C for 20" 72° for 1' 72° for 3' *cycles 2-4 repeated 35 times	CTGTTCAAC AGGGCTGGT TGGCAAC (127)	ATCATGTCTA GACTCATGGT GATCC (128)	890bp	Brain

Example 7
Protocol: Direct Identification of Inverse Agonists and Agonists

A. [^{35}S]GTPγS Assay

Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. Preferably, then, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. We have determined that when such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification of candidate compounds. Thus, it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

1. Membrane Preparation

Membranes comprising the constitutively active orphan GPCR Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists, agonists or partial agonists are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4; "Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4; "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM $MgCl_2$, pH 7.4

b. Procedure

All materials will be kept on ice throughout the procedure. Firstly, the media will be aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold

PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer will be added to scrape cells; this will be followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant will be aspirated and the pellet will be resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant will then be aspirated and the pellet resuspended in Binding Buffer. This will then be homogenized using a Brinkman polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

2. Bradford Protein Assay

Following the homogenization, protein concentration of the membranes will be determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and frozen (-80°C) for later use; when frozen, protocol for use will be as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a polytron at about 12 x 1,000 rpm for about 5-10 seconds; it was noted that for multiple preparations, the homogenizor should be thoroughly cleaned between homoginezation of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard will be utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

Duplicate tubes will be prepared, one including the membrane, and one as a control "blank". Each contained 800ul Binding Buffer. Thereafter, 10µl of Bradford Protein Standard (1mg/ml) will be added to each tube, and 10µl of membrane Protein

will then be added to just one tube (not the blank). Thereafter, 200ul of Bradford Dye Reagent will be added to each tube, followed by vortex of each. After five (5) minutes, the tubes will be re-vortexed and the material therein will be transferred to cuvettes. The cuvettes will then be read using a CECIL 3041 spectrophotometer, at wavelength 595.

3. Direct Identification Assay

a. Materials

GDP Buffer consisted of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 μM GDP (final concentration of GDP in each well was 0.1 μM GDP); each well comprising a candidate compound, has a final volume of 200ul consisting of 100μl GDP Buffer (final concentration, 0.1μM GDP), 50ul Membrane Protein in Binding Buffer, and 50μl [^{35}S]GTPγS (0.6 nM) in Binding Buffer (2.5 μl [^{35}S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds will be preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), will be homogenized briefly until in suspension. Protein concentration will then be determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) will then be diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5μg/well). Thereafter, 100 μl GDP Buffer was added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool will then be used to transfer 5 μl of a candidate compound into such well (*i.e.*, 5μl in total assay volume of 200 μl is a 1:40 ratio such that the final screening concentration of the candidate compound is 10μM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X)

and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 µl of Membrane Protein will be added to each well (a control well comprising membranes without the GPCR Fusion Protein was also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50µl of [^{35}S]GTPγS (0.6 nM) in Binding Buffer will be added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay will then be stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates will then be aspirated with an 8 channel manifold and sealed with plate covers. The plates will then be read on a Wallacc 1450 using setting "Prot. #37" (as per manufacturer instructions).

B. Cyclic AMP Assay

Another assay approach to directly identified candidate compound was accomplished by utilizing a cyclase-based assay. In addition to direct identification, this assay approach can be utilized as an independent approach to provide confirmation of the results from the [^{35}S]GTPγS approach as set forth above.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) was preferably utilized for direct identification of candidate compounds as inverse agonists and agonists to constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected cells were harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM $MgCl_2$. Homogenization was performed on ice using a Brinkman Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C., The resulting pellet was then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA,

homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet was then stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet as slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCL2, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 µCi of tracer [^{125}I cAMP (100 µl] to 11 ml Detection Buffer) were prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer was prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM $MgCl_2$, 20mM phospocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 µM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer was then stored on ice until utilized.

Candidate compounds identified as per above (if frozen, thawed at room temperature) were added, preferably, to 96-well plate wells (3µl/well; 12µM final assay concentration), together with 40 µl Membrane Protein (30µg/well) and 50µl of Assay Buffer. This admixture was then incubated for 30 minutes at room temperature, with gentle shaking.

Following the incubation, 100µl of Detection Buffer was added to each well, followed by incubation for 2-24 hours. Plates were then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

A representative screening assay plate (96 well format) result is presented in Figure 12. Each bar represents the results for a different compound in each well, plus RUP13-Gsα Fusion Protein construct, as prepared in Example 5(a) above. The representative results presented in Figure 12 also provide standard deviations based upon the mean results of each plate ("m") and the mean plus two arbitrary preference for

selection of inverse agonists as "leads" from the primary screen involves selection of candidate compounds that that reduce the per cent response by at least the mean plate response, minus two standard deviations. Conversely, an arbitrary preference for selection of an agonists as "leads" from the primary screen involves selection of candidate compounds that increase the per cent response by at least the mean plate response, plus the two standard deviations. Based upon these selection processes, the candidate compounds in the following wells were directly identified as putative inverse agonist (Compound A) and agonist (Compound B) to RUP13 in wells A2 and G9, respectively. *See,* Figure 12. It is noted for clarity: these compounds have been directly identified without any knowledge of the endogenous ligand for this GPCR. By focusing on assay techniques that are based upon receptor function, and not compound binding affinity, we are able to ascertain compounds that are able to reduce the functional activity of this receptor (Compound A) as well as increase the functional activity of the receptor (Compound B). Based upon the location of these receptor in lung tissue (see, for example, hRUP13 and hRUP21 in Example 6), pharmaceutical agents can be developed for potential therapeutic treatment of lung cancer.

References cited throughout this patent document, including co-pending and related patent applications, unless otherwise indicated, are fully incorporated herein by reference. Modifications and extension of the disclosed inventions that are within the purview of the skilled artisan are encompassed within the above disclosure and the claims that follow.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University

Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be viable. The ATCC has assigned the following deposit number to pCMV: ATCC #203351.

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CLAIMS

What is claimed is:

1. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:2.

2. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 1.

3. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:1.

4. A host cell comprising the plasmid of claim 3.

5. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:4.

6. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 5.

7. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:3.

8. A host cell comprising the plasmid of claim 7.

9. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:6.

10. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 9.

11. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:5.

12. A host cell comprising the plasmid of claim 11.

13. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:8.

14. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 13.

15. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:7.

16. A host cell comprising the plasmid of claim 15.

17. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:10.

18. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 17.

19. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:9.

20. A host cell comprising the plasmid of claim 19.

21. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:12.

22. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 21 comprising an amino acid sequence of SEQ.ID.NO.84.

23. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:11.

24. A host cell comprising the plasmid of claim 23.

25. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:14.

26. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 25 comprising an amino acid sequence of SEQ.ID.NO.88.

27. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:13.

28. A host cell comprising the plasmid of claim 27.

29. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:16.

30. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 29 comprising an amino acid sequence of SEQ.ID.NO.:92.

31. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:15.

32. A host cell comprising the plasmid of claim 31.

33. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:18.

34. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 33.

35. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:17.

36. A host cell comprising the plasmid of claim 35.

37. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:20.

38. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 37.

39. A plasmid comprising a vector and the cDNA of SE.ID.NO.:19.

40. A host cell comprising the plasmid of claim 39.

41. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:22.

42. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 41.

43. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:21.

44. A host cell comprising the plasmid of claim 43.

45. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:24.

46. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 45.

47. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:23.

48. A host cell comprising the plasmid of claim 47.

49. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:26.

50. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 49.

51. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:25.

52. A host cell comprising the plasmid of claim 51.

53. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:28.

54. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 53.

55. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:27.

56. A host cell comprising the plasmid of claim 55.

57. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:30.

58. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 57.

59. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:29.

60. A host cell comprising the plasmid of claim 59.

61. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:32.

62. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 61 comprising an amino acid sequence of SEQ.ID.NO.:96.

63. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:95.

64. A host cell comprising the plasmid of claim 63.

65. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:34.

66. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 65.

67. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:33.

68. A host cell comprising the plasmid of claim 67.

69. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:36.

70. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 69.

71. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:35.

72. A host cell comprising the plasmid of claim 71.

73. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:38.

74. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 73.

75. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:37.

76. A host cell comprising the plasmid of claim 75.

77. A G protein-coupled receptor encoded by an amino acid sequence of SEQ.ID.NO.:40.

78. A non-endogenous, constitutively activated version of the G protein-coupled receptor of claim 77.

79. A plasmid comprising a vector and the cDNA of SEQ.ID.NO.:39.

80. A host cell comprising the plasmid of claim 79.

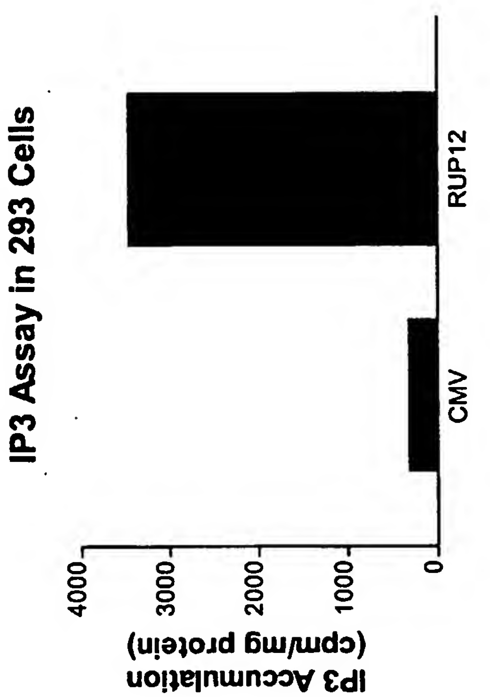

IP3 Assay in 293 Cells
IP3 Accumulation (cpm/mg protein)
4000
3000
2000
1000
0
CMV
RUP12

Figure 1

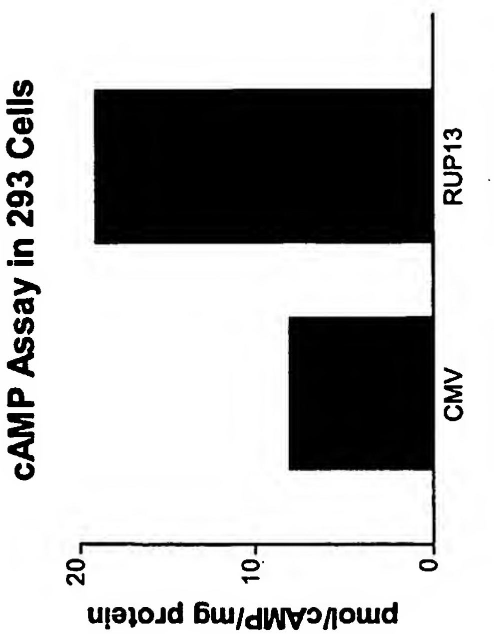


Figure 2

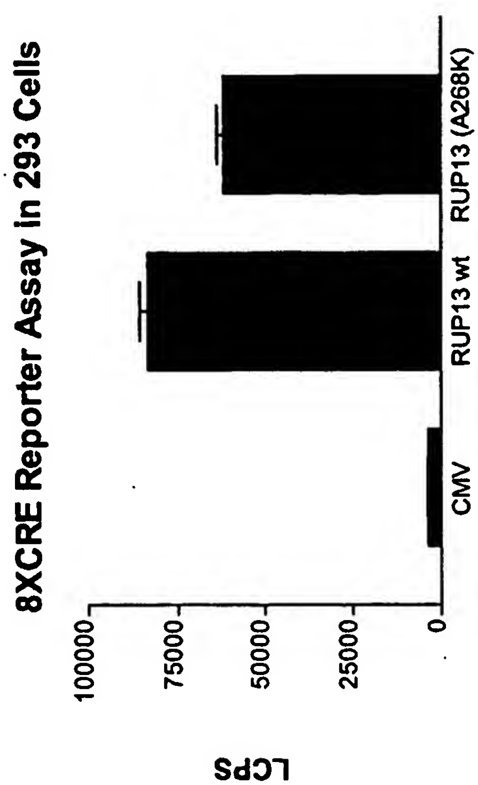

8XCRE Reporter Assay in 293 Cells
LCPS
100000
75000
50000
25000
0
CMV
RUP13 wt
RUP13 (A268K)

Figure 3

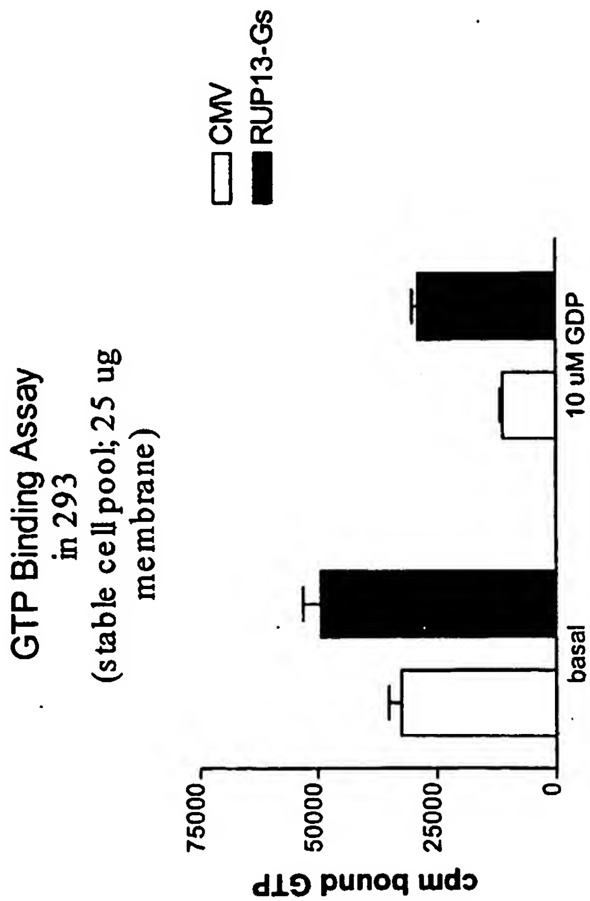

GTP Binding Assay
in 293
(stable cell pool; 25 ug
membrane)
CMV
RUP13-Gs
cpm bound GTP
75000
50000
25000
0
basal
10 uM GDP

Figure 4

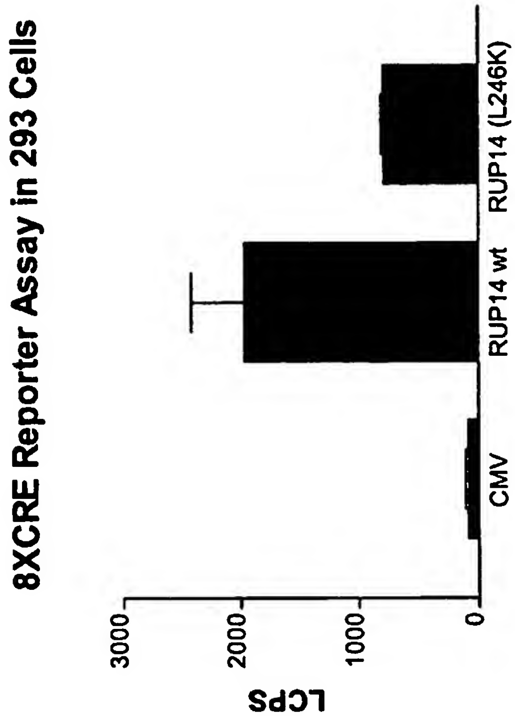

8XCRE Reporter Assay in 293 Cells
LCPS
3000
2000
1000
0
CMV
RUP14 wt
RUP14 (L246K)

Figure 5

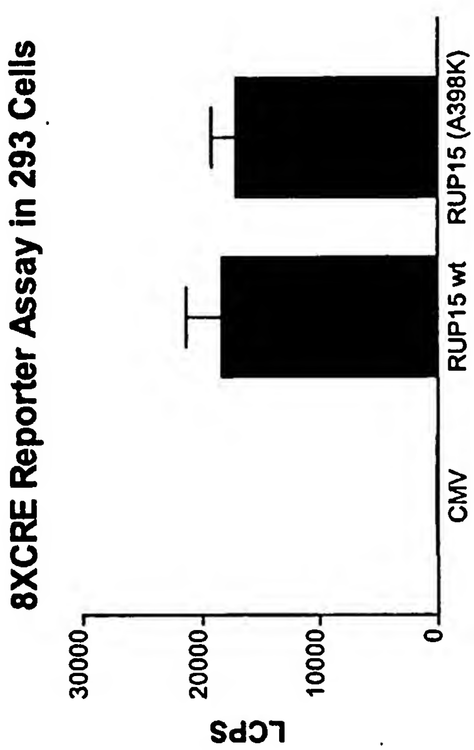

8XCRE Reporter Assay in 293 Cells
LCPS
30000
20000
10000
0
CMV
RUP15 wt
RUP15 (A398K)

Figure 6

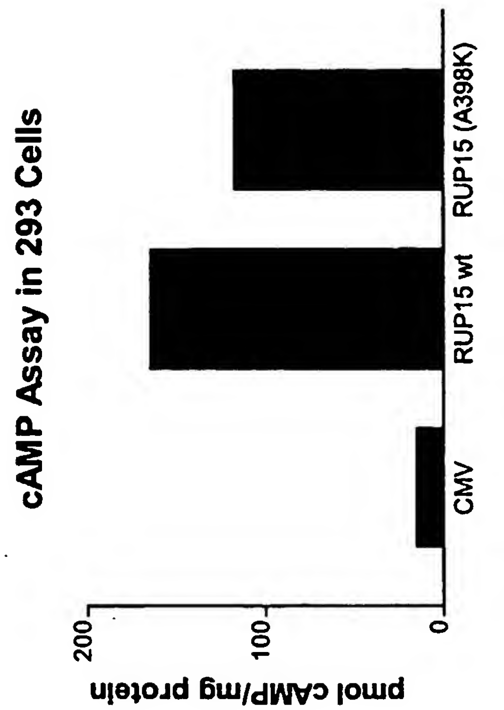
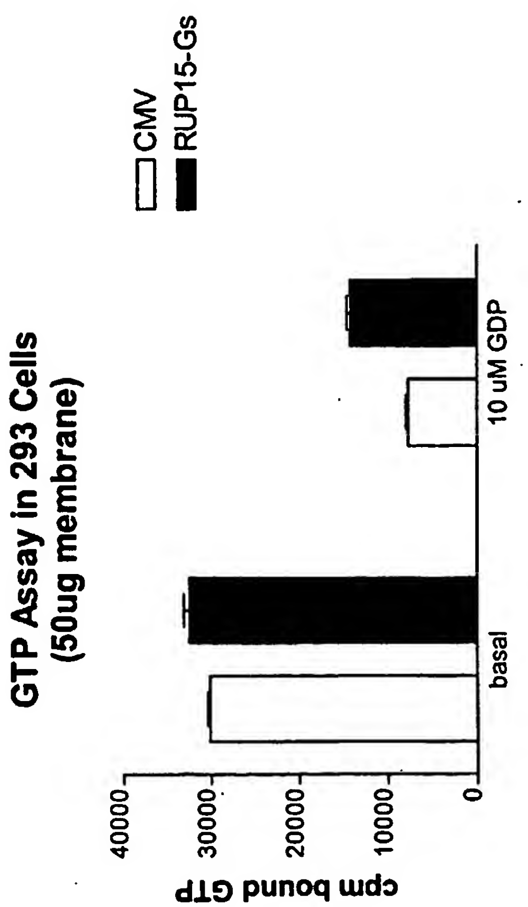

cAMP Assay in 293 Cells
pmol cAMP/mg protein
200
100
0
CMV
RUP15 wt
RUP15 (A398K)

Figure 7


GTP Assay in 293 Cells
(50ug membrane)
CMV
RUP15-Gs
cpm bound GTP
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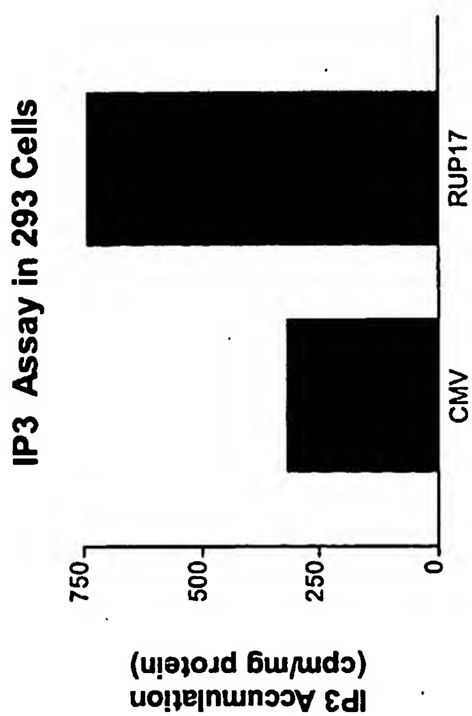
30000
20000
10000
0
basal
10 uM GDP

Figure 8


IP3 Assay in 293 Cells
IP3 Accumulation
(cpm/mg protein)
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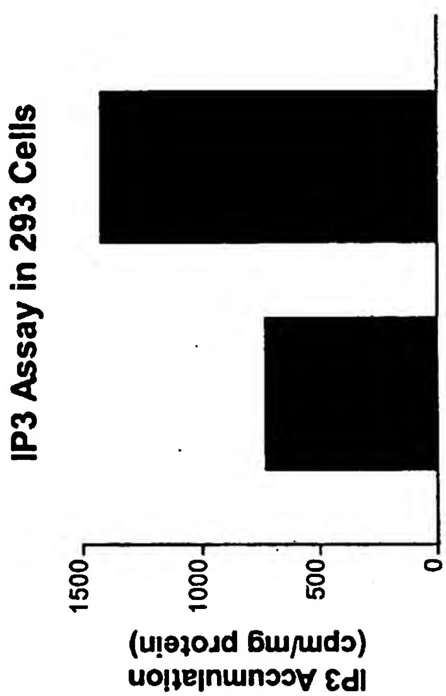
500
250
0
CMV
RUP17

Figure 9


IP3 Assay in 293 Cells
IP3 Accumulation
(cpm/mg protein)
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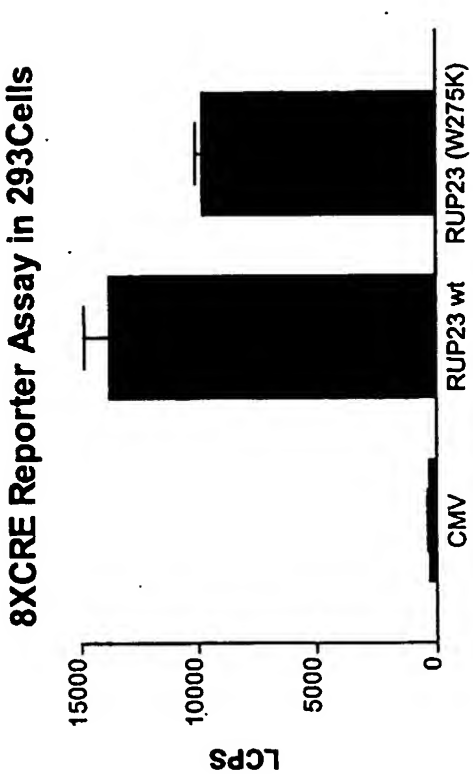
1000
500
0
CMV
RUP21

Figure 10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LCPS
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10000
5000
0
CMV
RUP23 wt
RUP23 (W275K)

Figure 11

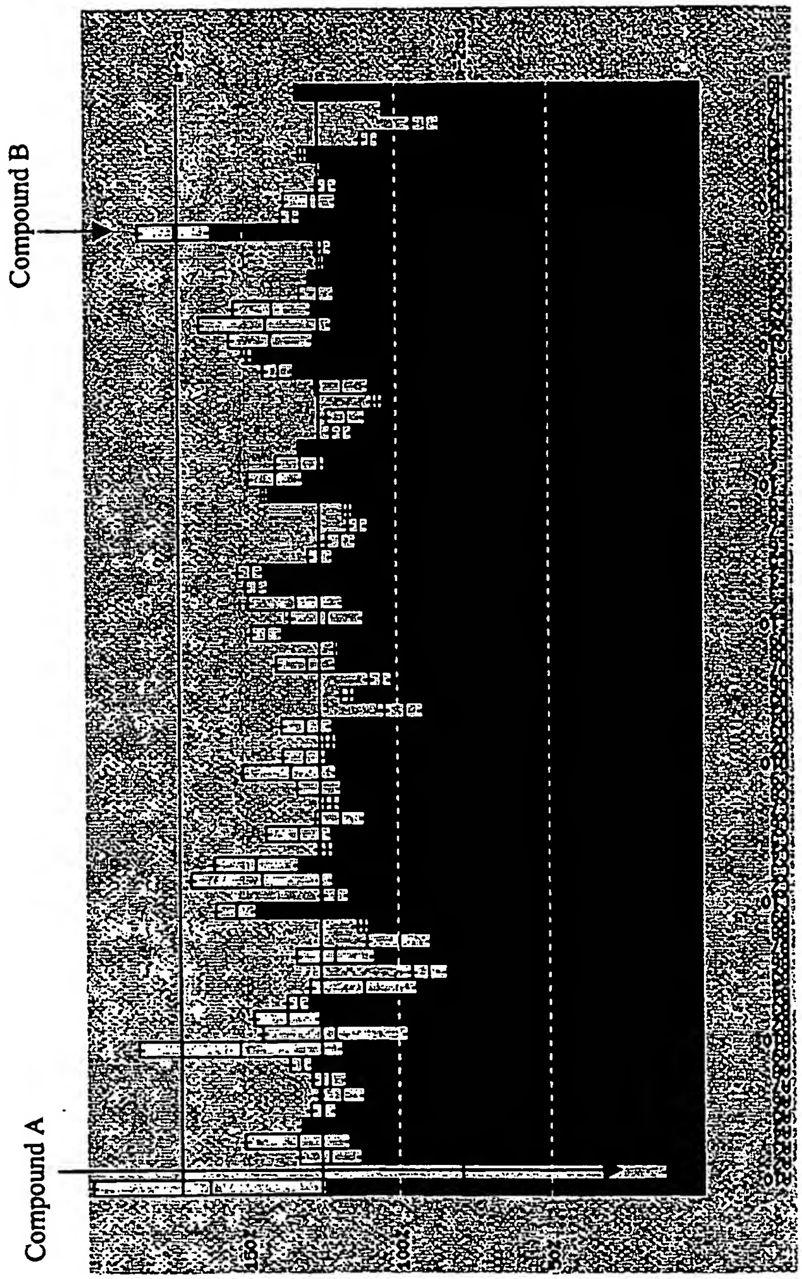

Figure 12

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Dang, Huong T.
Lowitz, Kevin P.

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Phe Phe Ala Ala Lys Ile Val Ile Gly Ile Ala Leu Ala Gly Ile Met
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Leu Val Cys Gly Ile Gly Asn Phe Val Phe Ile Ala Ala Leu Thr Arg
65                  70                  75                  80

Tyr Lys Lys Leu Arg Asn Leu Thr Asn Leu Leu Ile Ala Asn Leu Ala
                85                  90                  95

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Val Trp Met Val Ser Ile Leu Ile Ala Ile Pro Ser Ala Tyr Phe Ala
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Thr Glu Thr Val Leu Phe Ile Val Lys Ser Gln Glu Lys Ile Phe Cys
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35 40 45

Val Gly Phe Val Gly Asn Leu Cys Val Ile Gly Ile Leu Leu His Asn
50 55 60

Ala Trp Lys Gly Lys Pro Ser Met Ile His Ser Leu Ile Leu Asn Leu
65 70 75 80

Ser Leu Ala Asp Leu Ser Leu Leu Leu Phe Ser Ala Pro Ile Arg Ala
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Thr Ile Arg His His Glu Gly Val Glu Met Cys Leu Val Asp Val Pro
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195 200 205

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Trp Lys Trp Met Ile Thr Lys Lys Pro Pro Thr Val Ser Glu Ser Gln
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Ser Ser Gly Lys Gly Lys Thr Glu Lys Ala Glu Ile Pro Ile Leu Pro
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Asp Val Glu Gln Phe Trp His Glu Arg Asp Thr Val Pro Ser Val Gln
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Gly Val Pro Gly Asn Ala Met Val Ala Trp Val Ala Gly Lys Val Ala
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Leu Leu Cys Cys Leu Ser Leu Pro Ile Leu Ala Val Pro Ile Ala Arg
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Glu Pro Leu Ile Val Gly Leu Ala Leu Ala His Ser Cys Leu Asn Pro
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65                  70                  75                  80

Gly Pro Cys His Pro Thr Ser Ser Ser Leu Val Ser Ala Phe Leu Ala
                85                  90                  95

Pro Ile Leu Ala Leu Glu Phe Val Leu Gly Leu Val Gly Asn Ser Leu
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Ala Leu Phe Ile Phe Cys Ile His Thr Arg Pro Trp Thr Ser Asn Thr
        115                 120                 125

Val Phe Leu Val Ser Leu Val Ala Ala Asp Phe Leu Leu Ile Ser Asn
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Leu Pro Leu Arg Val Asp Tyr Tyr Leu Leu His Glu Thr Trp Arg Phe
145                 150                 155                 160

Gly Ala Ala Ala Cys Lys Val Asn Leu Phe Met Leu Ser Thr Asn Arg
                165                 170                 175

Thr Ala Ser Val Val Phe Leu Thr Ala Ile Ala Leu Asn Arg Tyr Leu
            180                 185                 190

Lys Val Val Gln Pro His His Val Leu Ser Arg Ala Ser Val Gly Ala
        195                 200                 205

Ala Ala Arg Val Ala Gly Gly Leu Trp Val Gly Ile Leu Leu Leu Asn
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Gly His Leu Leu Leu Ser Thr Phe Ser Gly Pro Ser Cys Leu Ser Tyr
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Arg Val Gly Thr Lys Pro Ser Ala Ser Leu Arg Trp His Gln Ala Leu
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Tyr Leu Leu Glu Phe Phe Leu Pro Leu Ala Leu Ile Leu Phe Ala Ile
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Val Ser Ile Gly Leu Thr Ile Arg Asn Arg Gly Leu Gly Gly Gln Ala
        275                 280                 285

Gly Pro Gln Arg Ala Met Arg Val Leu Ala Met Val Val Ala Val Tyr
    290                 295                 300

Thr Ile Cys Phe Leu Pro Ser Ile Ile Phe Gly Met Ala Ser Met Val
305                 310                 315                 320

Ala Phe Trp Leu Ser Ala Cys Arg Ser Leu Asp Leu Cys Thr Gln Leu
                325                 330                 335

Phe His Gly Ser Leu Ala Phe Thr Tyr Leu Asn Ser Val Leu Asp Pro
            340                 345                 350

Val Leu Tyr Cys Phe Ser Ser Pro Asn Phe Leu His Gln Ser Arg Ala
        355                 360                 365
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Ser Tyr Gln Pro Ser Arg Gln Trp Arg Tyr Arg Glu Ala Ser Arg Lys
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acccagcgct gtctctctgt cctcttccct atctggttca agtgtcaccg gcccaggcac 420

ctgtcagcct gggtgtgtgg cctgctgtgg acactctgtc tcctgatgaa cgggttgacc 480

tcttccttct gcagcaagtt cttgaaattc aatgaagatc ggtgcttcag ggtggacatg 540

gtccaggccg ccctcatcat gggggtctta accccagtga tgactctgtc cagcctgacc 600

ctctttgtct gggtgcggag gagctcccag cagtggcggc ggcagcccac acggctgttc 660

gtggtggtcc tggcctctgt cctggtgttc ctcatctgtt ccctgcctct gagcatctac 720

tggtttgtgc tctactggtt gagcctgccg cccgagatgc aggtcctgtg cttcagcttg 780

tcacgcctct cctcgtccgt aagcagcagc gccaaccccg tcatctactt cctggtgggc 840

agccggagga gccacaggct gcccaccagg tccctgggga ctgtgctcca acaggcgctt 900

cgcgaggagc ccgagctgga aggtggggag acgcccaccg tgggcaccaa tgagatgggg 960

gcttga 966

<210> 10
<211> 321
<212> PRT
<213> Homo sapiens

<400> 10

Met Asn Gln Thr Leu Asn Ser Ser Gly Thr Val Glu Ser Ala Leu Asn
1   5   10   15

Tyr Ser Arg Gly Ser Thr Val His Thr Ala Tyr Leu Val Leu Ser Ser
            20   25   30

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Leu Ala Met Phe Thr Cys Leu Cys Gly Met Ala Gly Asn Ser Met Val
        35                  40                  45

Ile Trp Leu Leu Gly Phe Arg Met His Arg Asn Pro Phe Cys Ile Tyr
    50                  55                  60

Ile Leu Asn Leu Ala Ala Ala Asp Leu Leu Phe Leu Phe Ser Met Ala
65                  70                  75                  80

Ser Thr Leu Ser Leu Glu Thr Gln Pro Leu Val Asn Thr Thr Asp Lys
                85                  90                  95

Val His Glu Leu Met Lys Arg Leu Met Tyr Phe Ala Tyr Thr Val Gly
            100                 105                 110

Leu Ser Leu Leu Thr Ala Ile Ser Thr Gln Arg Cys Leu Ser Val Leu
        115                 120                 125

Phe Pro Ile Trp Phe Lys Cys His Arg Pro Arg His Leu Ser Ala Trp
    130                 135                 140

Val Cys Gly Leu Leu Trp Thr Leu Cys Leu Leu Met Asn Gly Leu Thr
145                 150                 155                 160

Ser Ser Phe Cys Ser Lys Phe Leu Lys Phe Asn Glu Asp Arg Cys Phe
                165                 170                 175

Arg Val Asp Met Val Gln Ala Ala Leu Ile Met Gly Val Leu Thr Pro
            180                 185                 190

Val Met Thr Leu Ser Ser Leu Thr Leu Phe Val Trp Val Arg Arg Ser
        195                 200                 205

Ser Gln Gln Trp Arg Arg Gln Pro Thr Arg Leu Phe Val Val Val Leu
    210                 215                 220

Ala Ser Val Leu Val Phe Leu Ile Cys Ser Leu Pro Leu Ser Ile Tyr
225                 230                 235                 240

Trp Phe Val Leu Tyr Trp Leu Ser Leu Pro Pro Glu Met Gln Val Leu
                245                 250                 255

Cys Phe Ser Leu Ser Arg Leu Ser Ser Ser Val Ser Ser Ser Ala Asn
            260                 265                 270

Pro Val Ile Tyr Phe Leu Val Gly Ser Arg Arg Ser His Arg Leu Pro
        275                 280                 285

Thr Arg Ser Leu Gly Thr Val Leu Gln Gln Ala Leu Arg Glu Glu Pro
    290                 295                 300

Glu Leu Glu Gly Gly Glu Thr Pro Thr Val Gly Thr Asn Glu Met Gly
305                 310                 315                 320

Ala


<210>  11
<211>  1356
<212>  DNA
<213>  Homo sapiens

<400>  11
atggagtcct cacccatccc ccagtcatca gggaactctt ccactttggg gagggtccct        60
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tcggaatctg tggccctctt cttcatgctc ctgctggact tgactgctgt ggctggcaat 180

gccgctgtga tggccgtgat cgccaagacg cctgccctcc gaaaatttgt cttcgtcttc 240

cacctctgcc tggtggacct gctggctgcc ctgaccctca tgcccctggc catgctctcc 300

agctctgccc tctttgacca cgccctcttt ggggaggtgg cctgccgcct ctacttgttt 360

ctgagcgtgt gctttgtcag cctggccatc ctctcggtgt cagccatcaa tgtggagcgc 420

tactattacg tagtccaccc catgcgctac gaggtgcgca tgacgctggg gctggtggcc 480

tctgtgctgg tgggtgtgtg ggtgaaggcc ttggccatgg cttctgtgcc agtgttggga 540

agggtctcct gggaggaagg agctcccagt gtcccccag gctgttcact ccagtggagc 600

cacagtgcct actgccagct ttttgtggtg gtctttgctg tcctttactt tctgttgccc 660

ctgctcctca tacttgtggt ctactgcagc atgttccgag tggcccgcgt ggctgccatg 720

cagcacgggc cgctgcccac gtggatggag acaccccggc aacgctccga atctctcagc 780

agccgctcca cgatggtcac cagctcgggg gccccccaga ccaccccaca ccggacgttt 840

gggggaggga aagcagcagt ggttctcctg gctgtggggg gacagttcct gctctgttgg 900

ttgccctact tctctttcca cctctatgtt gccctgagtg ctcagcccat ttcaactggg 960

caggtggaga gtgtggtcac ctggattggc tacttttgct tcacttccaa ccctttcttc 1020

tatggatgtc tcaaccggca gatccggggg gagctcagca agcagtttgt ctgcttcttc 1080

aagccagctc cagaggagga gctgaggctg cctagccggg agggctccat tgaggagaac 1140

ttcctgcagt tccttcaggg gactggctgt ccttctgagt cctgggtttc ccgacccta 1200

cccagcccca agcaggagcc acctgctgtt gactttcgaa tcccaggcca gatagctgag 1260

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ctccgtcctg ccgcctcacc ccggctggag tcatga 1356

<210> 12
<211> 451
<212> PRT
<213> Homo sapiens

<400> 12

Met Glu Ser Ser Pro Ile Pro Gln Ser Ser Gly Asn Ser Ser Thr Leu
1 5 10 15

Gly Arg Val Pro Gln Thr Pro Gly Pro Ser Thr Ala Ser Gly Val Pro
20 25 30

Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
35 40 45

Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
50 55 60

```
Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
65                  70                  75                  80

His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
                85                  90                  95

Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
            100                 105                 110

Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
        115                 120                 125

Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
    130                 135                 140

Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
145                 150                 155                 160

Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
                165                 170                 175

Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
            180                 185                 190

Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
        195                 200                 205

Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Leu Ile
    210                 215                 220

Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
225                 230                 235                 240

Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
                245                 250                 255

Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
            260                 265                 270

Gln Thr Thr Pro His Arg Thr Phe Gly Gly Gly Lys Ala Ala Val Val
        275                 280                 285

Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe
    290                 295                 300

Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly
305                 310                 315                 320

Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser
                325                 330                 335

Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu
            340                 345                 350

Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu
        355                 360                 365

Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe
    370                 375                 380

Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu
385                 390                 395                 400

Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly
                405                 410                 415
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Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser
420 425 430

Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg
435 440 445

Leu Glu Ser
450

<210> 13
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 13
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ggcaccttca gcaataacaa cagcaggaac tgcacaattg aaaacttcaa gagagaattt 120

ttcccaattg tatatctgat aatatttttc tggggagtct tgggaaatgg gttgtccata 180

tatgttttcc tgcagcctta taagaagtcc acatctgtga acgttttcat gctaaatctg 240

gccatttcag atctcctgtt cataagcacg cttcccttca gggctgacta ttatcttaga 300

ggctccaatt ggatatttgg agacctggcc tgcaggatta tgtcttattc cttgtatgtc 360

aacatgtaca gcagtattta tttcctgacc gtgctgagtg ttgtgcgttt cctggcaatg 420

gttcacccct ttcggcttct gcatgtcacc agcatcagga gtgcctggat cctctgtggg 480

atcatatgga tccttatcat ggcttcctca ataatgctcc tggacagtgg ctctgagcag 540

aacggcagtg tcacatcatg cttagagctg aatctctata aaattgctaa gctgcagacc 600

atgaactata ttgccttggt ggtgggctgc ctgctgccat ttttcacact cagcatctgt 660

tatctgctga tcattcgggt tctgttaaaa gtggaggtcc cagaatcggg gctgcgggtt 720

tctcacagga aggcactgac caccatcatc atcaccttga tcatcttctt cttgtgtttc 780

ctgccctatc acacactgag gaccgtccac ttgacgacat ggaaagtggg tttatgcaaa 840

gacagactgc ataaagcttt ggttatcaca ctggccttgg cagcagccaa tgcctgcttc 900

aatcctctgc tctattactt tgctggggag aatttttaagg acagactaaa gtctgcactc 960

agaaaaggcc atccacagaa ggcaaagaca aagtgtgttt tccctgttag tgtgtggttg 1020

agaaaggaaa caagagtata a 1041

<210> 14
<211> 346
<212> PRT
<213> Homo sapiens

<400> 14

Met Glu Arg Lys Phe Met Ser Leu Gln Pro Ser Ile Ser Val Ser Glu
1 5 10 15

Met Glu Pro Asn Gly Thr Phe Ser Asn Asn Asn Ser Arg Asn Cys Thr
20 25 30

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Ile Glu Asn Phe Lys Arg Glu Phe Phe Pro Ile Val Tyr Leu Ile Ile
        35                  40                  45

Phe Phe Trp Gly Val Leu Gly Asn Gly Leu Ser Ile Tyr Val Phe Leu
    50                  55                  60

Gln Pro Tyr Lys Lys Ser Thr Ser Val Asn Val Phe Met Leu Asn Leu
65                  70                  75                  80

Ala Ile Ser Asp Leu Leu Phe Ile Ser Thr Leu Pro Phe Arg Ala Asp
                85                  90                  95

Tyr Tyr Leu Arg Gly Ser Asn Trp Ile Phe Gly Asp Leu Ala Cys Arg
            100                 105                 110

Ile Met Ser Tyr Ser Leu Tyr Val Asn Met Tyr Ser Ser Ile Tyr Phe
        115                 120                 125

Leu Thr Val Leu Ser Val Val Arg Phe Leu Ala Met Val His Pro Phe
    130                 135                 140

Arg Leu Leu His Val Thr Ser Ile Arg Ser Ala Trp Ile Leu Cys Gly
145                 150                 155                 160

Ile Ile Trp Ile Leu Ile Met Ala Ser Ser Ile Met Leu Leu Asp Ser
                165                 170                 175

Gly Ser Glu Gln Asn Gly Ser Val Thr Ser Cys Leu Glu Leu Asn Leu
            180                 185                 190

Tyr Lys Ile Ala Lys Leu Gln Thr Met Asn Tyr Ile Ala Leu Val Val
        195                 200                 205

Gly Cys Leu Leu Pro Phe Phe Thr Leu Ser Ile Cys Tyr Leu Leu Ile
    210                 215                 220

Ile Arg Val Leu Leu Lys Val Glu Val Pro Glu Ser Gly Leu Arg Val
225                 230                 235                 240

Ser His Arg Lys Ala Leu Thr Thr Ile Ile Ile Thr Leu Ile Ile Phe
                245                 250                 255

Phe Leu Cys Phe Leu Pro Tyr His Thr Leu Arg Thr Val His Leu Thr
            260                 265                 270

Thr Trp Lys Val Gly Leu Cys Lys Asp Arg Leu His Lys Ala Leu Val
        275                 280                 285

Ile Thr Leu Ala Leu Ala Ala Ala Asn Ala Cys Phe Asn Pro Leu Leu
    290                 295                 300

Tyr Tyr Phe Ala Gly Glu Asn Phe Lys Asp Arg Leu Lys Ser Ala Leu
305                 310                 315                 320

Arg Lys Gly His Pro Gln Lys Ala Lys Thr Lys Cys Val Phe Pro Val
                325                 330                 335

Ser Val Trp Leu Arg Lys Glu Thr Arg Val
            340                 345
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<210> 15
<211> 1527
<212> DNA
<213> Homo sapiens

<400> 15
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ctctccaaaa tgcccatcag cctggcccac ggcatcatcc gctcaaccgt gctggttatc 120

ttcctcgccg cctctttcgt cggcaacata gtgctggcgc tagtgttgca gcgcaagccg 180

cagctgctgc aggtgaccaa ccgttttatc tttaacctcc tcgtcaccga cctgctgcag 240

atttcgctcg tggccccctg ggtggtggcc acctctgtgc ctctcttctg gcccctcaac 300

agccacttct gcacggccct ggttagcctc acccacctgt tcgccttcgc cagcgtcaac 360

accattgtcg tggtgtcagt ggatcgctac ttgtccatca tccaccctct ctcctacccg 420

tccaagatga cccagcgccg cggttacctg ctcctctatg gcacctggat tgtggccatc 480

ctgcagagca ctcctccact ctacggctgg ggccaggctg cctttgatga gcgcaatgct 540

ctctgctcca tgatctgggg ggccagcccc agctacacta ttctcagcgt ggtgtccttc 600

atcgtcattc cactgattgt catgattgcc tgctactccg tggtgttctg tgcagcccgg 660

aggcagcatg ctctgctgta caatgtcaag agacacagct tggaagtgcg agtcaaggac 720

tgtgtggaga atgaggatga agagggagca gagaagaagg aggagttcca ggatgagagt 780

gagtttcgcc gccagcatga aggtgaggtc aaggccaagg agggcagaat ggaagccaag 840

gacggcagcc tgaaggccaa ggaaggaagc acggggacca gtgagagtag tgtagaggcc 900

aggggcagcg aggaggtcag agagagcagc acggtggcca gcgacggcag catggagggt 960

aaggaaggca gcaccaaagt tgaggagaac agcatgaagg cagacaaggg tcgcacagag 1020

gtcaaccagt gcagcattga cttgggtgaa gatgacatgg agtttggtga agacgacatc 1080

aatttcagtg aggatgacgt cgaggcagtg aacatcccgg agagcctccc acccagtcgt 1140

cgtaacagca acagcaaccc tcctctgccc aggtgctacc agtgcaaagc tgctaaagtg 1200

atcttcatca tcattttctc ctatgtgcta tccctggggc cctactgctt tttagcagtc 1260

ctggccgtgt gggtggatgt cgaaacccag gtaccccagt gggtgatcac cataatcatc 1320

tggcttttct tcctgcagtg ctgcatccac ccctatgtct atggctacat gcacaagacc 1380

attaagaagg aaatccagga catgctgaag aagttcttct gcaaggaaaa gcccccgaaa 1440

gaagatagcc acccagacct gcccggaaca gagggtggga ctgaaggcaa gattgtccct 1500

tcctacgatt ctgctacttt tccttga 1527

<210> 16
<211> 508
<212> PRT
<213> Homo sapiens

<400> 16

Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His
1 5 10 15

Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile
20 25 30

Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly
35 40 45

Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln
50 55 60

Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln
65 70 75 80

Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe
85 90 95

Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His
100 105 110

Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp
115 120 125

Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr
130 135 140

Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile
145 150 155 160

Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp
165 170 175

Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr
180 185 190

Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
195 200 205

Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
210 215 220

Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
225 230 235 240

Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
245 250 255

Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
260 265 270

Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
275 280 285

Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
290 295 300

Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
305 310 315 320

Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
325 330 335

Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
340 345 350

Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
355 360 365

Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
370 375 380

Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Ala Lys Val
385 390 395 400

Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
405 410 415

Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
420 425 430

Gln Trp Val Ile Thr Ile Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
435 440 445

Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
450 455 460

Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
465 470 475 480

Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
485 490 495

Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro
500 505

<210> 17
<211> 1068
<212> DNA
<213> Homo sapiens

<400> 17
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atatttgtct gggttatagc tttcattacc tgctttggaa atctttttgt cattggcatg 120

agatctttca ttaaagctga aaatacaact cacgctatgt ccatcaaaat cctttgttgc 180

gctgattgcc tgatgggtgt ttacttgttc tttgttggca ttttcgatat aaaataccga 240

gggcagtatc agaagtatgc cttgctgtgg atggagagcg tgcagtgccg cctcatgggg 300

ttcctggcca tgctgtccac cgaagtctct gttctgctac tgacctactt gactttggag 360

aagttcctgg tcattgtctt ccccttcagt aacattcgac ctggaaaacg gcagacctca 420

gtcatcctca tttgcatctg gatggcggga tttttaatag ctgtaattcc attttggaat 480

aaggattatt ttggaaactt ttatgggaaa aatggagtat gtttcccact ttattatgac 540

caaacagaag atattggaag caaagggtat tctcttggaa ttttcctagg tgtgaacttg 600

ctggcttttc tcatcattgt gttttcctat attactatgt tctgttccat tcaaaaaacc 660

gccttgcaga ccacagaagt aaggaattgt tttggaagag aggtggctgt tgcaaatcgt 720

ttcttttta tagtgttctc tgatgccatc tgctggattc ctgtatttgt agttaaaatc 780

ctttccctct tccgggtgga aataccagac acaatgactt cctggatagt gatttttttc 840

cttccagtta acagtgcttt gaatccaatc ctctatactc tcacaaccaa ctttttaag 900

gacaagttga aacagctgct gcacaaacat cagaggaaat caattttcaa aattaaaaaa 960

aaaagtttat ctacatccat tgtgtggata gaggactcct cttccctgaa acttggggtt 1020

ttgaacaaaa taacacttgg agacagtata atgaaaccag tttcctag 1068

<210> 18
<211> 355
<212> PRT
<213> Homo sapiens

<400> 18

Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn
1 5 10 15

Asn Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe
20 25 30

Gly Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn
35 40 45

Thr Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu
50 55 60

Met Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg
65 70 75 80

Gly Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys
85 90 95

Arg Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu
100 105 110

Leu Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro
115 120 125

Phe Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile
130 135 140

Cys Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn
145 150 155 160

Lys Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro
165 170 175

Leu Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu
180 185 190

Gly Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe
195 200 205

Ser Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr
210 215 220

Thr Glu Val Arg Asn Cys Phe Gly Arg Glu Val Ala Val Ala Asn Arg
225 230 235 240

Phe Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe
245 250 255

Val Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro Asp Thr Met
260 265 270

Thr Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser Ala Leu Asn

275 280 285

Pro Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp Lys Leu Lys
290 295 300

Gln Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys Ile Lys Lys
305 310 315 320

Lys Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser Ser Ser Leu
325 330 335

Lys Leu Gly Val Leu Asn Lys Ile Thr Leu Gly Asp Ser Ile Met Lys
340 345 350

Pro Val Ser
355

<210> 19
<211> 969
<212> DNA
<213> Homo sapiens

<400> 19
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actctttgct acaagcagac cttgagcctc acggtgctga cgtgcatcgt ttcccttgtc 120

gggctgacag gaaacgcagt tgtgctctgg ctcctgggct gccgcatgcg caggaacgcc 180

ttctccatct acatcctcaa cttggccgca gcagacttcc tcttcctcag cggccgcctt 240

atatattccc tgttaagctt catcagtatc ccccatacca tctctaaaat cctctatcct 300

gtgatgatgt tttcctactt tgcaggcctg agctttctga gtgccgtgag caccgagcgc 360

tgcctgtccg tcctgtggcc catctggtac cgctgccacc gccccacaca cctgtcagcg 420

gtggtgtgtg tcctgctctg ggccctgtcc ctgctgcgga gcatcctgga gtggatgtta 480

tgtggcttcc tgttcagtgg tgctgattct gcttggtgtc aaacatcaga tttcatcaca 540

gtcgcgtggc tgattttttt atgtgtggtt ctctgtgggt ccagcctggt cctgctgatc 600

aggattctct gtggatcccg gaagataccg ctgaccaggc tgtacgtgac catcctgctc 660

acagtactgg tcttcctcct ctgtggcctg ccctttggca ttcagttttt cctattttta 720

tggatccacg tggacaggga agtcttattt tgtcatgttc atctagtttc tattttcctg 780

tccgctctta acagcagtgc caaccccatc atttacttct tcgtgggctc ctttaggcag 840

cgtcaaaata ggcagaacct gaagctggtt ctccagaggg ctctgcagga cgcgtctgag 900

gtggatgaag gtggagggca gcttcctgag gaaatcctgg agctgtcggg aagcagattg 960

gagcagtga 969

<210> 20
<211> 322
<212> PRT
<213> Homo sapiens

<400> 20

```
Met Asp Pro Thr Ile Ser Thr Leu Asp Thr Glu Leu Thr Pro Ile Asn
1               5                   10                  15

Gly Thr Glu Glu Thr Leu Cys Tyr Lys Gln Thr Leu Ser Leu Thr Val
            20                  25                  30

Leu Thr Cys Ile Val Ser Leu Val Gly Leu Thr Gly Asn Ala Val Val
        35                  40                  45

Leu Trp Leu Leu Gly Cys Arg Met Arg Arg Asn Ala Phe Ser Ile Tyr
    50                  55                  60

Ile Leu Asn Leu Ala Ala Ala Asp Phe Leu Phe Leu Ser Gly Arg Leu
65                  70                  75                  80

Ile Tyr Ser Leu Leu Ser Phe Ile Ser Ile Pro His Thr Ile Ser Lys
                85                  90                  95

Ile Leu Tyr Pro Val Met Met Phe Ser Tyr Phe Ala Gly Leu Ser Phe
            100                 105                 110

Leu Ser Ala Val Ser Thr Glu Arg Cys Leu Ser Val Leu Trp Pro Ile
        115                 120                 125

Trp Tyr Arg Cys His Arg Pro Thr His Leu Ser Ala Val Val Cys Val
    130                 135                 140

Leu Leu Trp Ala Leu Ser Leu Leu Arg Ser Ile Leu Glu Trp Met Leu
145                 150                 155                 160

Cys Gly Phe Leu Phe Ser Gly Ala Asp Ser Ala Trp Cys Gln Thr Ser
                165                 170                 175

Asp Phe Ile Thr Val Ala Trp Leu Ile Phe Leu Cys Val Val Leu Cys
            180                 185                 190

Gly Ser Ser Leu Val Leu Leu Ile Arg Ile Leu Cys Gly Ser Arg Lys
        195                 200                 205

Ile Pro Leu Thr Arg Leu Tyr Val Thr Ile Leu Leu Thr Val Leu Val
    210                 215                 220

Phe Leu Leu Cys Gly Leu Pro Phe Gly Ile Gln Phe Phe Leu Phe Leu
225                 230                 235                 240

Trp Ile His Val Asp Arg Glu Val Leu Phe Cys His Val His Leu Val
                245                 250                 255

Ser Ile Phe Leu Ser Ala Leu Asn Ser Ser Ala Asn Pro Ile Ile Tyr
            260                 265                 270

Phe Phe Val Gly Ser Phe Arg Gln Arg Gln Asn Arg Gln Asn Leu Lys
        275                 280                 285

Leu Val Leu Gln Arg Ala Leu Gln Asp Ala Ser Glu Val Asp Glu Gly
    290                 295                 300

Gly Gly Gln Leu Pro Glu Glu Ile Leu Glu Leu Ser Gly Ser Arg Leu
305                 310                 315                 320

Glu Gln

<210>  21
<211>  1305
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<212> DNA
<213> Homo sapiens

<400> 21
atggaggatc tctttagccc ctcaattctg ccgccggcgc ccaacatttc cgtgcccatc 60

ttgctgggct ggggtctcaa cctgaccttg gggcaaggag cccctgcctc tgggccgccc 120

agccgccgcg tccgcctggt gttcctgggg gtcatcctgg tggtggcggt ggcaggcaac 180

accacagtgc tgtgccgcct gtgcggcggc ggcgggccct gggcgggccc caagcgtcgc 240

aagatggact tcctgctggt gcagctggcc ctggcggacc tgtacgcgtg cgggggcacg 300

gcgctgtcac agctggcctg ggaactgctg ggcgagcccc gcgcggccac gggggacctg 360

gcgtgccgct tcctgcagct gctgcaggca tccgggcggg gcgcctcggc ccacctcgtg 420

gtgctcatcg ccctcgagcg ccggcgcgcg gtgcgtcttc cgcacggccg gccgctgccc 480

gcgcgtgccc tcgccgccct gggctggctg ctggcactgc tgctggcgct gcccccggcc 540

ttcgtggtgc gcggggactc cccctcgccg ctgccgccgc cgccgccgcc aacgtccctg 600

cagccaggcg cgcccccggc cgcccgcgcc tggccggggg agcgtcgctg ccacgggatc 660

ttcgcgcccc tgccgcgctg gcacctgcag gtctacgcgt tctacgaggc cgtcgcgggc 720

ttcgtcgcgc ctgttacggt cctgggcgtc gcttgcggcc acctactctc cgtctggtgg 780

cggcaccggc cgcaggcccc cgcggctgca gcgccctggt cggcgagccc aggtcgagcc 840

cctgcgccca gcgcgctgcc ccgcgccaag gtgcagagcc tgaagatgag cctgctgctg 900

gcgctgctgt tcgtgggctg cgagctgccc tactttgccg cccggctggc ggccgcgtgg 960

tcgtccgggc ccgcgggaga ctgggaggga gagggcctgt cggcggcgct gcgcgtggtg 1020

gcgatggcca acagcgctct caatcccttc gtctacctct tcttccaggc gggcgactgc 1080

cggctccggc gacagctgcg gaagcggctg ggctctctgt gctgcgcgcc gcagggaggc 1140

gcggaggacg aggaggggcc ccggggccac caggcgctct accgccaacg ctggccccac 1200

cctcattatc accatgctcg gcgggaaccg ctggacgagg gcggcttgcg cccacccccct 1260

ccgcgcccca gacccctgcc ttgctcctgc gaaagtgcct tctag 1305

<210> 22
<211> 434
<212> PRT
<213> Homo sapiens

<400> 22

Met Glu Asp Leu Phe Ser Pro Ser Ile Leu Pro Pro Ala Pro Asn Ile
1 5 10 15

Ser Val Pro Ile Leu Leu Gly Trp Gly Leu Asn Leu Thr Leu Gly Gln
20 25 30

Gly Ala Pro Ala Ser Gly Pro Pro Ser Arg Arg Val Arg Leu Val Phe
35 40 45

Leu Gly Val Ile Leu Val Val Ala Val Ala Gly Asn Thr Thr Val Leu
    50   55   60

Cys Arg Leu Cys Gly Gly Gly Gly Pro Trp Ala Gly Pro Lys Arg Arg
65   70   75   80

Lys Met Asp Phe Leu Leu Val Gln Leu Ala Leu Ala Asp Leu Tyr Ala
                85   90   95

Cys Gly Gly Thr Ala Leu Ser Gln Leu Ala Trp Glu Leu Leu Gly Glu
            100   105   110

Pro Arg Ala Ala Thr Gly Asp Leu Ala Cys Arg Phe Leu Gln Leu Leu
        115   120   125

Gln Ala Ser Gly Arg Gly Ala Ser Ala His Leu Val Val Leu Ile Ala
    130   135   140

Leu Glu Arg Arg Arg Ala Val Arg Leu Pro His Gly Arg Pro Leu Pro
145   150   155   160

Ala Arg Ala Leu Ala Ala Leu Gly Trp Leu Leu Ala Leu Leu Leu Ala
                165   170   175

Leu Pro Pro Ala Phe Val Val Arg Gly Asp Ser Pro Ser Pro Leu Pro
            180   185   190

Pro Pro Pro Pro Pro Thr Ser Leu Gln Pro Gly Ala Pro Pro Ala Ala
        195   200   205

Arg Ala Trp Pro Gly Glu Arg Arg Cys His Gly Ile Phe Ala Pro Leu
    210   215   220

Pro Arg Trp His Leu Gln Val Tyr Ala Phe Tyr Glu Ala Val Ala Gly
225   230   235   240

Phe Val Ala Pro Val Thr Val Leu Gly Val Ala Cys Gly His Leu Leu
                245   250   255

Ser Val Trp Trp Arg His Arg Pro Gln Ala Pro Ala Ala Ala Ala Pro
            260   265   270

Trp Ser Ala Ser Pro Gly Arg Ala Pro Ala Pro Ser Ala Leu Pro Arg
        275   280   285

Ala Lys Val Gln Ser Leu Lys Met Ser Leu Leu Leu Ala Leu Leu Phe
    290   295   300

Val Gly Cys Glu Leu Pro Tyr Phe Ala Ala Arg Leu Ala Ala Ala Trp
305   310   315   320

Ser Ser Gly Pro Ala Gly Asp Trp Glu Gly Glu Gly Leu Ser Ala Ala
                325   330   335

Leu Arg Val Val Ala Met Ala Asn Ser Ala Leu Asn Pro Phe Val Tyr
            340   345   350

Leu Phe Phe Gln Ala Gly Asp Cys Arg Leu Arg Arg Gln Leu Arg Lys
        355   360   365

Arg Leu Gly Ser Leu Cys Cys Ala Pro Gln Gly Gly Ala Glu Asp Glu
    370   375   380

Glu Gly Pro Arg Gly His Gln Ala Leu Tyr Arg Gln Arg Trp Pro His
385   390   395   400

Pro His Tyr His His Ala Arg Arg Glu Pro Leu Asp Glu Gly Gly Leu
405 410 415

Arg Pro Pro Pro Pro Arg Pro Arg Pro Leu Pro Cys Ser Cys Glu Ser
420 425 430

Ala Phe

<210> 23
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 23
atgtacaacg ggtcgtgctg ccgcatcgag ggggacacca tctcccaggt gatgccgccg 60

ctgctcattg tggcctttgt gctgggcgca ctaggcaatg gggtcgccct gtgtggtttc 120

tgcttccaca tgaagacctg gaagcccagc actgtttacc ttttcaattt ggccgtggct 180

gatttcctcc ttatgatctg cctgcctttt cggacagact attacctcag acgtagacac 240

tgggcttttg gggacattcc ctgccgagtg gggctcttca cgttggccat gaacagggcc 300

gggagcatcg tgttccttac ggtggtggct gcggacaggt atttcaaagt ggtccacccc 360

caccacgcgg tgaacactat ctccacccgg gtggcggctg gcatcgtctg caccctgtgg 420

gccctggtca tcctgggaac agtgtatctt ttgctggaga accatctctg cgtgcaagag 480

acggccgtct cctgtgagag cttcatcatg gagtcggcca atggctggca tgacatcatg 540

ttccagctgg agttctttat gcccctcggc atcatcttat tttgctcctt caagattgtt 600

tggagcctga ggcggaggca gcagctggcc agacaggctc ggatgaagaa ggcgacccgg 660

ttcatcatgg tggtggcaat tgtgttcatc acatgctacc tgcccagcgt gtctgctaga 720

ctctatttcc tctggacggt gccctcgagt gcctgcgatc cctctgtcca tggggccctg 780

cacataaccc tcagcttcac ctacatgaac agcatgctgg atcccctggt gtattatttt 840

tcaagcccct cctttcccaa attctacaac aagctcaaaa tctgcagtct gaaacccaag 900

cagccaggac actcaaaaac acaaaggccg gaagagatgc caatttcgaa cctcggtcgc 960

aggagttgca tcagtgtggc aaatagtttc caaagccagt ctgatgggca atgggatccc 1020

cacattgttg agtggcactg a 1041

<210> 24
<211> 346
<212> PRT
<213> Homo sapiens

<400> 24

Met Tyr Asn Gly Ser Cys Cys Arg Ile Glu Gly Asp Thr Ile Ser Gln
1 5 10 15

Val Met Pro Pro Leu Leu Ile Val Ala Phe Val Leu Gly Ala Leu Gly
20 25 30

```
Asn Gly Val Ala Leu Cys Gly Phe Cys Phe His Met Lys Thr Trp Lys
        35                  40                  45

Pro Ser Thr Val Tyr Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu
    50                  55                  60

Met Ile Cys Leu Pro Phe Arg Thr Asp Tyr Tyr Leu Arg Arg Arg His
65                  70                  75                  80

Trp Ala Phe Gly Asp Ile Pro Cys Arg Val Gly Leu Phe Thr Leu Ala
                85                  90                  95

Met Asn Arg Ala Gly Ser Ile Val Phe Leu Thr Val Val Ala Ala Asp
            100                 105                 110

Arg Tyr Phe Lys Val Val His Pro His His Ala Val Asn Thr Ile Ser
        115                 120                 125

Thr Arg Val Ala Ala Gly Ile Val Cys Thr Leu Trp Ala Leu Val Ile
    130                 135                 140

Leu Gly Thr Val Tyr Leu Leu Leu Glu Asn His Leu Cys Val Gln Glu
145                 150                 155                 160

Thr Ala Val Ser Cys Glu Ser Phe Ile Met Glu Ser Ala Asn Gly Trp
                165                 170                 175

His Asp Ile Met Phe Gln Leu Glu Phe Phe Met Pro Leu Gly Ile Ile
            180                 185                 190

Leu Phe Cys Ser Phe Lys Ile Val Trp Ser Leu Arg Arg Arg Gln Gln
        195                 200                 205

Leu Ala Arg Gln Ala Arg Met Lys Lys Ala Thr Arg Phe Ile Met Val
    210                 215                 220

Val Ala Ile Val Phe Ile Thr Cys Tyr Leu Pro Ser Val Ser Ala Arg
225                 230                 235                 240

Leu Tyr Phe Leu Trp Thr Val Pro Ser Ser Ala Cys Asp Pro Ser Val
                245                 250                 255

His Gly Ala Leu His Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
            260                 265                 270

Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Lys Phe
        275                 280                 285

Tyr Asn Lys Leu Lys Ile Cys Ser Leu Lys Pro Lys Gln Pro Gly His
    290                 295                 300

Ser Lys Thr Gln Arg Pro Glu Glu Met Pro Ile Ser Asn Leu Gly Arg
305                 310                 315                 320

Arg Ser Cys Ile Ser Val Ala Asn Ser Phe Gln Ser Gln Ser Asp Gly
                325                 330                 335

Gln Trp Asp Pro His Ile Val Glu Trp His
            340                 345
```

<210> 25
<211> 1011
<212> DNA
<213> Homo sapiens

<400> 25
atgaacaaca atacaacatg tattcaacca tctatgatct cttccatggc tttaccaatc 60

atttacatcc tcctttgtat tgttggtgtt tttggaaaca ctctctctca atggatattt 120

ttaacaaaaa taggtaaaaa aacatcaacg cacatctacc tgtcacacct tgtgactgca 180

aacttacttg tgtgcagtgc catgcctttc atgagtatct atttcctgaa aggtttccaa 240

tgggaatatc aatctgctca atgcagagtg gtcaattttc tgggaactct atccatgcat 300

gcaagtatgt ttgtcagtct cttaatttta agttggattg ccataagccg ctatgctacc 360

ttaatgcaaa aggattcctc gcaagagact acttcatgct atgagaaaat attttatggc 420

catttactga aaaaatttcg ccagcccaac tttgctagaa aactatgcat ttacatatgg 480

ggagttgtac tgggcataat cattccagtt accgtatact actcagtcat agaggctaca 540

gaaggagaag agagcctatg ctacaatcgg cagatggaac taggagccat gatctctcag 600

attgcaggtc tcattggaac cacatttatt ggattttcct ttttagtagt actaacatca 660

tactactctt ttgtaagcca tctgagaaaa ataagaacct gtacgtccat tatggagaaa 720

gatttgactt acagttctgt gaaaagacat cttttggtca tccagattct actaatagtt 780

tgcttccttc cttatagtat ttttaaaccc atttttttatg ttctacacca aagagataac 840

tgtcagcaat tgaattattt aatagaaaca aaaaacattc tcacctgtct tgcttcggcc 900

agaagtagca cagaccccat tatatttctt ttattagata aaacattcaa gaagacacta 960

tataatctct ttacaaagtc taattcagca catatgcaat catatggttg a 1011

<210> 26
<211> 336
<212> PRT
<213> Homo sapiens

<400> 26

Met Asn Asn Asn Thr Thr Cys Ile Gln Pro Ser Met Ile Ser Ser Met
1 5 10 15

Ala Leu Pro Ile Ile Tyr Ile Leu Leu Cys Ile Val Gly Val Phe Gly
20 25 30

Asn Thr Leu Ser Gln Trp Ile Phe Leu Thr Lys Ile Gly Lys Lys Thr
35 40 45

Ser Thr His Ile Tyr Leu Ser His Leu Val Thr Ala Asn Leu Leu Val
50 55 60

Cys Ser Ala Met Pro Phe Met Ser Ile Tyr Phe Leu Lys Gly Phe Gln
65 70 75 80

Trp Glu Tyr Gln Ser Ala Gln Cys Arg Val Val Asn Phe Leu Gly Thr
85 90 95

Leu Ser Met His Ala Ser Met Phe Val Ser Leu Leu Ile Leu Ser Trp
100 105 110

Ile Ala Ile Ser Arg Tyr Ala Thr Leu Met Gln Lys Asp Ser Ser Gln
115 120 125

Glu Thr Thr Ser Cys Tyr Glu Lys Ile Phe Tyr Gly His Leu Leu Lys
130 135 140

Lys Phe Arg Gln Pro Asn Phe Ala Arg Lys Leu Cys Ile Tyr Ile Trp
145 150 155 160

Gly Val Val Leu Gly Ile Ile Ile Pro Val Thr Val Tyr Tyr Ser Val
165 170 175

Ile Glu Ala Thr Glu Gly Glu Glu Ser Leu Cys Tyr Asn Arg Gln Met
180 185 190

Glu Leu Gly Ala Met Ile Ser Gln Ile Ala Gly Leu Ile Gly Thr Thr
195 200 205

Phe Ile Gly Phe Ser Phe Leu Val Val Leu Thr Ser Tyr Tyr Ser Phe
210 215 220

Val Ser His Leu Arg Lys Ile Arg Thr Cys Thr Ser Ile Met Glu Lys
225 230 235 240

Asp Leu Thr Tyr Ser Ser Val Lys Arg His Leu Leu Val Ile Gln Ile
245 250 255

Leu Leu Ile Val Cys Phe Leu Pro Tyr Ser Ile Phe Lys Pro Ile Phe
260 265 270

Tyr Val Leu His Gln Arg Asp Asn Cys Gln Gln Leu Asn Tyr Leu Ile
275 280 285

Glu Thr Lys Asn Ile Leu Thr Cys Leu Ala Ser Ala Arg Ser Ser Thr
290 295 300

Asp Pro Ile Ile Phe Leu Leu Leu Asp Lys Thr Phe Lys Lys Thr Leu
305 310 315 320

Tyr Asn Leu Phe Thr Lys Ser Asn Ser Ala His Met Gln Ser Tyr Gly
325 330 335

<210> 27
<211> 1014
<212> DNA
<213> Homo sapiens

<400> 27
atgaatgagc cactagacta tttagcaaat gcttctgatt tccccgatta tgcagctgct 60

tttggaaatt gcactgatga aaacatccca ctcaagatgc actacctccc tgttatttat 120

ggcattatct tcctcgtggg atttccaggc aatgcagtag tgatatccac ttacattttc 180

aaaatgagac cttggaagag cagcaccatc attatgctga acctggcctg cacagatctg 240

ctgtatctga ccagcctccc cttcctgatt cactactatg ccagtggcga aaactggatc 300

tttggagatt tcatgtgtaa gtttatccgc ttcagcttcc atttcaacct gtatagcagc 360

atcctcttcc tcacctgttt cagcatcttc cgctactgtg tgatcattca cccaatgagc 420

tgcttttcca ttcacaaaac tcgatgtgca gttgtagcct gtgctgtggt gtggatcatt 480

tcactggtag ctgtcattcc gatgaccttc ttgatcacat caaccaacag gaccaacaga 540

tcagcctgtc tcgacctcac cagttcggat gaactcaata ctattaagtg gtacaacctg 600

attttgactg caactacttt ctgcctcccc ttggtgatag tgacactttg ctataccacg 660

attatccaca ctctgaccca tggactgcaa actgacagct gccttaagca gaaagcacga 720

aggctaacca ttctgctact ccttgcattt tacgtatgtt ttttaccctt ccatatcttg 780

agggtcattc ggatcgaatc tcgcctgctt tcaatcagtt gttccattga gaatcagatc 840

catgaagctt acatcgtttc tagaccatta gctgctctga acacctttgg taacctgtta 900

ctatatgtgg tggtcagcga caactttcag caggctgtct gctcaacagt gagatgcaaa 960

gtaagcggga accttgagca agcaaagaaa attagttact caaacaaccc ttga 1014

<210> 28
<211> 337
<212> PRT
<213> Homo sapiens

<400> 28

Met Asn Glu Pro Leu Asp Tyr Leu Ala Asn Ala Ser Asp Phe Pro Asp
1 5 10 15

Tyr Ala Ala Ala Phe Gly Asn Cys Thr Asp Glu Asn Ile Pro Leu Lys
20 25 30

Met His Tyr Leu Pro Val Ile Tyr Gly Ile Ile Phe Leu Val Gly Phe
35 40 45

Pro Gly Asn Ala Val Val Ile Ser Thr Tyr Ile Phe Lys Met Arg Pro
50 55 60

Trp Lys Ser Ser Thr Ile Ile Met Leu Asn Leu Ala Cys Thr Asp Leu
65 70 75 80

Leu Tyr Leu Thr Ser Leu Pro Phe Leu Ile His Tyr Tyr Ala Ser Gly
85 90 95

Glu Asn Trp Ile Phe Gly Asp Phe Met Cys Lys Phe Ile Arg Phe Ser
100 105 110

Phe His Phe Asn Leu Tyr Ser Ser Ile Leu Phe Leu Thr Cys Phe Ser
115 120 125

Ile Phe Arg Tyr Cys Val Ile Ile His Pro Met Ser Cys Phe Ser Ile
130 135 140

His Lys Thr Arg Cys Ala Val Val Ala Cys Ala Val Val Trp Ile Ile
145 150 155 160

Ser Leu Val Ala Val Ile Pro Met Thr Phe Leu Ile Thr Ser Thr Asn
165 170 175

Arg Thr Asn Arg Ser Ala Cys Leu Asp Leu Thr Ser Ser Asp Glu Leu
180 185 190

Asn Thr Ile Lys Trp Tyr Asn Leu Ile Leu Thr Ala Thr Thr Phe Cys
195 200 205

Leu Pro Leu Val Ile Val Thr Leu Cys Tyr Thr Thr Ile Ile His Thr

```
    210                 215                 220

Leu Thr His Gly Leu Gln Thr Asp Ser Cys Leu Lys Gln Lys Ala Arg
225                 230                 235                 240

Arg Leu Thr Ile Leu Leu Leu Leu Ala Phe Tyr Val Cys Phe Leu Pro
                245                 250                 255

Phe His Ile Leu Arg Val Ile Arg Ile Glu Ser Arg Leu Leu Ser Ile
            260                 265                 270

Ser Cys Ser Ile Glu Asn Gln Ile His Glu Ala Tyr Ile Val Ser Arg
        275                 280                 285

Pro Leu Ala Ala Leu Asn Thr Phe Gly Asn Leu Leu Leu Tyr Val Val
    290                 295                 300

Val Ser Asp Asn Phe Gln Gln Ala Val Cys Ser Thr Val Arg Cys Lys
305                 310                 315                 320

Val Ser Gly Asn Leu Glu Gln Ala Lys Lys Ile Ser Tyr Ser Asn Asn
                325                 330                 335

Pro


<210>  29
<211>  993
<212>  DNA
<213>  Homo sapiens

<400>  29
atggatccaa ccaccccggc ctggggaaca gaaagtacaa cagtgaatgg aaatgaccaa      60

gcccttcttc tgctttgtgg caaggagacc ctgatcccgg tcttcctgat ccttttcatt     120

gccctggtcg ggctggtagg aaacgggttt gtgctctggc tcctgggctt ccgcatgcgc     180

aggaacgcct tctctgtcta cgtcctcagc ctggccgggg ccgacttcct cttcctctgc     240

ttccagatta taaattgcct ggtgtacctc agtaacttct tctgttccat ctccatcaat     300

ttccctagct tcttcaccac tgtgatgacc tgtgcctacc ttgcaggcct gagcatgctg     360

agcaccgtca gcaccgagcg ctgcctgtcc gtcctgtggc ccatctggta tcgctgccgc     420

cgccccagac acctgtcagc ggtcgtgtgt gtcctgctct gggccctgtc cctactgctg     480

agcatcttgg aagggaagtt ctgtggcttc ttatttagtg atggtgactc tggttggtgt     540

cagacatttg atttcatcac tgcagcgtgg ctgatttttt tattcatggt tctctgtggg     600

tccagtctgg ccctgctggt caggatcctc tgtggctcca ggggtctgcc actgaccagg     660

ctgtacctga ccatcctgct cacagtgctg gtgttcctcc tctgcggcct gccctttggc     720

attcagtggt tcctaatatt atggatctgg aaggattctg atgtcttatt ttgtcatatt     780

catccagttt cagttgtcct gtcatctctt aacagcagtg ccaaccccat catttacttc     840

ttcgtgggct cttttaggaa gcagtggcgg ctgcagcagc cgatcctcaa gctggctctc     900

cagagggctc tgcaggacat tgctgaggtg gatcacagtg aaggatgctt ccgtcagggc     960

accccggaga tgtcgagaag cagtctggtg tag                                  993
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<210> 30
<211> 330
<212> PRT
<213> Homo sapiens

<400> 30

Met Asp Pro Thr Thr Pro Ala Trp Gly Thr Glu Ser Thr Thr Val Asn
1 5 10 15

Gly Asn Asp Gln Ala Leu Leu Leu Leu Cys Gly Lys Glu Thr Leu Ile
20 25 30

Pro Val Phe Leu Ile Leu Phe Ile Ala Leu Val Gly Leu Val Gly Asn
35 40 45

Gly Phe Val Leu Trp Leu Leu Gly Phe Arg Met Arg Arg Asn Ala Phe
50 55 60

Ser Val Tyr Val Leu Ser Leu Ala Gly Ala Asp Phe Leu Phe Leu Cys
65 70 75 80

Phe Gln Ile Ile Asn Cys Leu Val Tyr Leu Ser Asn Phe Phe Cys Ser
85 90 95

Ile Ser Ile Asn Phe Pro Ser Phe Phe Thr Thr Val Met Thr Cys Ala
100 105 110

Tyr Leu Ala Gly Leu Ser Met Leu Ser Thr Val Ser Thr Glu Arg Cys
115 120 125

Leu Ser Val Leu Trp Pro Ile Trp Tyr Arg Cys Arg Arg Pro Arg His
130 135 140

Leu Ser Ala Val Val Cys Val Leu Leu Trp Ala Leu Ser Leu Leu Leu
145 150 155 160

Ser Ile Leu Glu Gly Lys Phe Cys Gly Phe Leu Phe Ser Asp Gly Asp
165 170 175

Ser Gly Trp Cys Gln Thr Phe Asp Phe Ile Thr Ala Ala Trp Leu Ile
180 185 190

Phe Leu Phe Met Val Leu Cys Gly Ser Ser Leu Ala Leu Leu Val Arg
195 200 205

Ile Leu Cys Gly Ser Arg Gly Leu Pro Leu Thr Arg Leu Tyr Leu Thr
210 215 220

Ile Leu Leu Thr Val Leu Val Phe Leu Leu Cys Gly Leu Pro Phe Gly
225 230 235 240

Ile Gln Trp Phe Leu Ile Leu Trp Ile Trp Lys Asp Ser Asp Val Leu
245 250 255

Phe Cys His Ile His Pro Val Ser Val Val Leu Ser Ser Leu Asn Ser
260 265 270

Ser Ala Asn Pro Ile Ile Tyr Phe Phe Val Gly Ser Phe Arg Lys Gln
275 280 285

Trp Arg Leu Gln Gln Pro Ile Leu Lys Leu Ala Leu Gln Arg Ala Leu
290 295 300

Gln Asp Ile Ala Glu Val Asp His Ser Glu Gly Cys Phe Arg Gln Gly
305 310 315 320

Thr Pro Glu Met Ser Arg Ser Ser Leu Val
325 330

<210> 31
<211> 1092
<212> DNA
<213> Homo sapiens

<400> 31
atgggccccg gcgaggcgct gctggcgggt ctcctggtga tggtactggc cgtggcgctg 60

ctatccaacg cactggtgct gctttgttgc gcctacagcg ctgagctccg cactcgagcc 120

tcaggcgtcc tcctggtgaa tctgtcgctg ggccacctgc tgctggcggc gctggacatg 180

cccttcacgc tgctcggtgt gatgcgcggg cggacaccgt cggcgcccgg cgcatgccaa 240

gtcattggct tcctggacac cttcctggcg tccaacgcgg cgctgagcgt ggcggcgctg 300

agcgcagacc agtggctggc agtgggcttc ccactgcgct acgccggacg cctgcgaccg 360

cgctatgccg gcctgctgct gggctgtgcc tggggacagt cgctggcctt ctcaggcgct 420

gcacttggct gctcgtggct tggctacagc agcgccttcg cgtcctgttc gctgcgcctg 480

ccgcccgagc ctgagcgtcc gcgcttcgca gccttcaccg ccacgctcca tgccgtgggc 540

ttcgtgctgc cgctggcggt gctctgcctc acctcgctcc aggtgcaccg ggtggcacgc 600

agccactgcc agcgcatgga caccgtcacc atgaaggcgc tcgcgctgct cgccgacctg 660

caccccagtg tgcggcagcg ctgcctcatc cagcagaagc ggcgccgcca ccgcgccacc 720

aggaagattg gcattgctat tgcgaccttc ctcatctgct ttgccccgta tgtcatgacc 780

aggctggcgg agctcgtgcc cttcgtcacc gtgaacgccc agtggggcat cctcagcaag 840

tgcctgacct acagcaaggc ggtggccgac ccgttcacgt actctctgct ccgccggccg 900

ttccgccaag tcctggccgg catggtgcac cggctgctga agagaacccc gcgcccagca 960

tccacccatg acagctctct ggatgtggcc ggcatggtgc accagctgct gaagagaacc 1020

ccgcgcccag cgtccaccca caacggctct gtggacacag agaatgattc ctgcctgcag 1080

cagacacact ga 1092

<210> 32
<211> 363
<212> PRT
<213> Homo sapiens

<400> 32

Met Gly Pro Gly Glu Ala Leu Leu Ala Gly Leu Leu Val Met Val Leu
1 5 10 15

Ala Val Ala Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Cys Ala Tyr
20 25 30

Ser Ala Glu Leu Arg Thr Arg Ala Ser Gly Val Leu Leu Val Asn Leu
35 40 45

Ser Leu Gly His Leu Leu Leu Ala Ala Leu Asp Met Pro Phe Thr Leu
50 55 60

Leu Gly Val Met Arg Gly Arg Thr Pro Ser Ala Pro Gly Ala Cys Gln
65 70 75 80

Val Ile Gly Phe Leu Asp Thr Phe Leu Ala Ser Asn Ala Ala Leu Ser
85 90 95

Val Ala Ala Leu Ser Ala Asp Gln Trp Leu Ala Val Gly Phe Pro Leu
100 105 110

Arg Tyr Ala Gly Arg Leu Arg Pro Arg Tyr Ala Gly Leu Leu Leu Gly
115 120 125

Cys Ala Trp Gly Gln Ser Leu Ala Phe Ser Gly Ala Ala Leu Gly Cys
130 135 140

Ser Trp Leu Gly Tyr Ser Ser Ala Phe Ala Ser Cys Ser Leu Arg Leu
145 150 155 160

Pro Pro Glu Pro Glu Arg Pro Arg Phe Ala Ala Phe Thr Ala Thr Leu
165 170 175

His Ala Val Gly Phe Val Leu Pro Leu Ala Val Leu Cys Leu Thr Ser
180 185 190

Leu Gln Val His Arg Val Ala Arg Ser His Cys Gln Arg Met Asp Thr
195 200 205

Val Thr Met Lys Ala Leu Ala Leu Leu Ala Asp Leu His Pro Ser Val
210 215 220

Arg Gln Arg Cys Leu Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr
225 230 235 240

Arg Lys Ile Gly Ile Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala Pro
245 250 255

Tyr Val Met Thr Arg Leu Ala Glu Leu Val Pro Phe Val Thr Val Asn
260 265 270

Ala Gln Trp Gly Ile Leu Ser Lys Cys Leu Thr Tyr Ser Lys Ala Val
275 280 285

Ala Asp Pro Phe Thr Tyr Ser Leu Leu Arg Arg Pro Phe Arg Gln Val
290 295 300

Leu Ala Gly Met Val His Arg Leu Leu Lys Arg Thr Pro Arg Pro Ala
305 310 315 320

Ser Thr His Asp Ser Ser Leu Asp Val Ala Gly Met Val His Gln Leu
325 330 335

Leu Lys Arg Thr Pro Arg Pro Ala Ser Thr His Asn Gly Ser Val Asp
340 345 350

Thr Glu Asn Asp Ser Cys Leu Gln Gln Thr His
355 360

<210> 33
<211> 1125

<212> DNA
<213> Homo sapiens

<400> 33
atgcccacac tcaatacttc tgcctctcca cccacattct tctgggccaa tgcctccgga 60

ggcagtgtgc tgagtgctga tgatgctccg atgcctgtca aattcctagc cctgaggctc 120

atggttgccc tggcctatgg gcttgtgggg gccattggct tgctgggaaa tttggcggtg 180

ctgtgggtac tgagtaactg tgcccggaga gcccctggcc caccttcaga caccttcgtc 240

ttcaacctgg ctctggcgga cctgggactg gcactcactc tcccctttg ggcagccgag 300

tcggcactgg actttcactg gcccttcgga ggtgccctct gcaagatggt tctgacggcc 360

actgtcctca acgtctatgc cagcatcttc ctcatcacag cgctgagcgt tgctcgctac 420

tgggtggtgg ccatggctgc ggggccaggc acccacctct cactcttctg ggcccgaata 480

gccaccctgg cagtgtgggc ggcggctgcc ctggtgacgg tgcccacagc tgtcttcggg 540

gtggagggtg aggtgtgtgg tgtgcgcctt tgcctgctgc gtttccccag caggtactgg 600

ctgggggcct accagctgca gagggtggtg ctggctttca tggtgccctt gggcgtcatc 660

accaccagct acctgctgct gctggccttc ctgcagcggc ggcaacggcg gcggcaggac 720

agcagggtcg tggcccgctc tgtccgcatc ctggtggctt ccttcttcct ctgctggttt 780

cccaaccatg tggtcactct ctggggtgtc ctggtgaagt ttgacctggt gccctggaac 840

agtactttct atactatcca gacgtatgtc ttccctgtca ctacttgctt ggcacacagc 900

aatagctgcc tcaaccctgt gctgtactgt ctcctgaggc gggagccccg gcaggctctg 960

gcaggcacct tcagggatct gcggtcgagg ctgtggcccc agggcggagg ctgggtgcaa 1020

caggtggccc taaagcaggt aggcaggcgg tgggtcgcaa gcaacccccg ggagagccgc 1080

ccttctaccc tgctcaccaa cctggacaga gggacacccg ggtga 1125

<210> 34
<211> 374
<212> PRT
<213> Homo sapiens

<400> 34

Met Pro Thr Leu Asn Thr Ser Ala Ser Pro Pro Thr Phe Phe Trp Ala
1 5 10 15

Asn Ala Ser Gly Gly Ser Val Leu Ser Ala Asp Asp Ala Pro Met Pro
20 25 30

Val Lys Phe Leu Ala Leu Arg Leu Met Val Ala Leu Ala Tyr Gly Leu
35 40 45

Val Gly Ala Ile Gly Leu Leu Gly Asn Leu Ala Val Leu Trp Val Leu
50 55 60

Ser Asn Cys Ala Arg Arg Ala Pro Gly Pro Pro Ser Asp Thr Phe Val
65 70 75 80

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Phe Asn Leu Ala Leu Ala Asp Leu Gly Leu Ala Leu Thr Leu Pro Phe
                85                  90                  95

Trp Ala Ala Glu Ser Ala Leu Asp Phe His Trp Pro Phe Gly Gly Ala
            100                 105                 110

Leu Cys Lys Met Val Leu Thr Ala Thr Val Leu Asn Val Tyr Ala Ser
        115                 120                 125

Ile Phe Leu Ile Thr Ala Leu Ser Val Ala Arg Tyr Trp Val Val Ala
    130                 135                 140

Met Ala Ala Gly Pro Gly Thr His Leu Ser Leu Phe Trp Ala Arg Ile
145                 150                 155                 160

Ala Thr Leu Ala Val Trp Ala Ala Ala Ala Leu Val Thr Val Pro Thr
                165                 170                 175

Ala Val Phe Gly Val Glu Gly Glu Val Cys Gly Val Arg Leu Cys Leu
            180                 185                 190

Leu Arg Phe Pro Ser Arg Tyr Trp Leu Gly Ala Tyr Gln Leu Gln Arg
        195                 200                 205

Val Val Leu Ala Phe Met Val Pro Leu Gly Val Ile Thr Thr Ser Tyr
    210                 215                 220

Leu Leu Leu Leu Ala Phe Leu Gln Arg Arg Gln Arg Arg Arg Gln Asp
225                 230                 235                 240

Ser Arg Val Val Ala Arg Ser Val Arg Ile Leu Val Ala Ser Phe Phe
                245                 250                 255

Leu Cys Trp Phe Pro Asn His Val Val Thr Leu Trp Gly Val Leu Val
            260                 265                 270

Lys Phe Asp Leu Val Pro Trp Asn Ser Thr Phe Tyr Thr Ile Gln Thr
        275                 280                 285

Tyr Val Phe Pro Val Thr Thr Cys Leu Ala His Ser Asn Ser Cys Leu
    290                 295                 300

Asn Pro Val Leu Tyr Cys Leu Leu Arg Arg Glu Pro Arg Gln Ala Leu
305                 310                 315                 320

Ala Gly Thr Phe Arg Asp Leu Arg Ser Arg Leu Trp Pro Gln Gly Gly
                325                 330                 335

Gly Trp Val Gln Gln Val Ala Leu Lys Gln Val Gly Arg Arg Trp Val
            340                 345                 350

Ala Ser Asn Pro Arg Glu Ser Arg Pro Ser Thr Leu Leu Thr Asn Leu
        355                 360                 365

Asp Arg Gly Thr Pro Gly
    370

<210>  35
<211>  1092
<212>  DNA
<213>  Homo sapiens

<400>  35
atgaatcggc accatctgca ggatcacttt ctggaaatag acaagaagaa ctgctgtgtg      60
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ttccgagatg acttcattgt caaggtgttg ccgccggtgt tggggctgga gtttatcttc 120

gggcttctgg gcaatggcct tgccctgtgg attttctgtt tccacctcaa gtcctggaaa 180

tccagccgga ttttcctgtt caacctggca gtggctgact ttctactgat catctgcctg 240

cccttcctga tggacaacta tgtgaggcgt tgggactgga agtttgggga catcccttgc 300

cggctgatgc tcttcatgtt ggctatgaac cgccagggca gcatcatctt cctcacggtg 360

gtggcggtag acaggtattt ccgggtggtc catccccacc acgccctgaa caagatctcc 420

aatcggacag cagccatcat ctcttgcctt ctgtggggca tcactattgg cctgacagtc 480

cacctcctga agaagaagat gccgatccag aatggcggtg caaatttgtg cagcagcttc 540

agcatctgcc ataccttcca gtggcacgaa gccatgttcc tcctggagtt cttcctgccc 600

ctgggcatca tcctgttctg ctcagccaga attatctgga gcctgcggca gagacaaatg 660

gaccggcatg ccaagatcaa gagagccatc accttcatca tggtggtggc catcgtcttt 720

gtcatctgct tccttcccag cgtggttgtg cggatccgca tcttctggct cctgcacact 780

tcgggcacgc agaattgtga agtgtaccgc tcggtggacc tggcgttctt tatcactctc 840

agcttcacct acatgaacag catgctggac cccgtggtgt actacttctc cagcccatcc 900

tttcccaact tcttctccac tttgatcaac cgctgcctcc agaggaagat gacaggtgag 960

ccagataata accgcagcac gagcgtcgag ctcacagggg accccaacaa aaccagaggc 1020

gctccagagg cgttaatggc caactccggt gagccatgga gcccctctta tctgggccca 1080

acctctcctt aa 1092

<210> 36
<211> 363
<212> PRT
<213> Homo sapiens

<400> 36

Met Asn Arg His His Leu Gln Asp His Phe Leu Glu Ile Asp Lys Lys
1 5 10 15

Asn Cys Cys Val Phe Arg Asp Asp Phe Ile Val Lys Val Leu Pro Pro
20 25 30

Val Leu Gly Leu Glu Phe Ile Phe Gly Leu Leu Gly Asn Gly Leu Ala
35 40 45

Leu Trp Ile Phe Cys Phe His Leu Lys Ser Trp Lys Ser Ser Arg Ile
50 55 60

Phe Leu Phe Asn Leu Ala Val Ala Asp Phe Leu Leu Ile Ile Cys Leu
65 70 75 80

Pro Phe Leu Met Asp Asn Tyr Val Arg Arg Trp Asp Trp Lys Phe Gly
85 90 95

Asp Ile Pro Cys Arg Leu Met Leu Phe Met Leu Ala Met Asn Arg Gln
100 105 110

```
Gly Ser Ile Ile Phe Leu Thr Val Val Ala Val Asp Arg Tyr Phe Arg
        115                 120                 125

Val Val His Pro His His Ala Leu Asn Lys Ile Ser Asn Arg Thr Ala
    130                 135                 140

Ala Ile Ile Ser Cys Leu Leu Trp Gly Ile Thr Ile Gly Leu Thr Val
145                 150                 155                 160

His Leu Leu Lys Lys Lys Met Pro Ile Gln Asn Gly Gly Ala Asn Leu
                165                 170                 175

Cys Ser Ser Phe Ser Ile Cys His Thr Phe Gln Trp His Glu Ala Met
            180                 185                 190

Phe Leu Leu Glu Phe Phe Leu Pro Leu Gly Ile Ile Leu Phe Cys Ser
        195                 200                 205

Ala Arg Ile Ile Trp Ser Leu Arg Gln Arg Gln Met Asp Arg His Ala
    210                 215                 220

Lys Ile Lys Arg Ala Ile Thr Phe Ile Met Val Val Ala Ile Val Phe
225                 230                 235                 240

Val Ile Cys Phe Leu Pro Ser Val Val Val Arg Ile Arg Ile Phe Trp
                245                 250                 255

Leu Leu His Thr Ser Gly Thr Gln Asn Cys Glu Val Tyr Arg Ser Val
            260                 265                 270

Asp Leu Ala Phe Phe Ile Thr Leu Ser Phe Thr Tyr Met Asn Ser Met
        275                 280                 285

Leu Asp Pro Val Val Tyr Tyr Phe Ser Ser Pro Ser Phe Pro Asn Phe
    290                 295                 300

Phe Ser Thr Leu Ile Asn Arg Cys Leu Gln Arg Lys Met Thr Gly Glu
305                 310                 315                 320

Pro Asp Asn Asn Arg Ser Thr Ser Val Glu Leu Thr Gly Asp Pro Asn
                325                 330                 335

Lys Thr Arg Gly Ala Pro Glu Ala Leu Met Ala Asn Ser Gly Glu Pro
            340                 345                 350

Trp Ser Pro Ser Tyr Leu Gly Pro Thr Ser Pro
        355                 360

<210>  37
<211>  1044
<212>  DNA
<213>  Homo sapiens

<400>  37
atgggggatg agctggcacc ttgccctgtg ggcactacag cttggccggc cctgatccag      60

ctcatcagca agacaccctg catgccccaa gcagccagca acacttcctt gggcctgggg     120

gacctcaggg tgcccagctc catgctgtac tggcttttcc ttccctcaag cctgctggct     180

gcagccacac tggctgtcag ccccctgctg ctggtgacca tcctgcggaa ccaacggctg     240

cgacaggagc cccactacct gctcccggct aacatcctgc tctcagacct ggcctacatt     300

ctcctccaca tgctcatctc ctccagcagc ctgggtggct gggagctggg ccgcatggcc     360
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tgtggcattc tcactgatgc tgtcttcgcc gcctgcacca gcaccatcct gtccttcacc     420
gccattgtgc tgcacaccta cctggcagtc atccatccac tgcgctacct ctccttcatg     480
tcccatgggg ctgcctggaa ggcagtggcc ctcatctggc tggtggcctg ctgcttcccc     540
acattcctta tttggctcag caagtggcag gatgcccagc tggaggagca aggagcttca     600
tacatcctac caccaagcat gggcacccag ccgggatgtg gcctcctggt cattgttacc     660
tacacctcca ttctgtgcgt tctgttcctc tgcacagctc tcattgccaa ctgtttctgg     720
aggatctatg cagaggccaa gacttcaggc atctgggggc agggctattc ccgggccagg     780
ggcaccctgc tgatccactc agtgctgatc acattgtacg tgagcacagg ggtggtgttc     840
tccctggaca tggtgctgac caggtaccac cacattgact ctgggactca cacatggctc     900
ctggcagcta acagtgaggt actcatgatg cttccccgtg ccatgctccc atacctgtac     960
ctgctccgct accggcagct gttgggcatg gtccggggcc acctcccatc caggaggcac    1020
caggccatct ttaccatttc ctag                                           1044
```

<210> 38
<211> 347
<212> PRT
<213> Homo sapiens

<400> 38

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Met Gly Asp Glu Leu Ala Pro Cys Pro Val Gly Thr Thr Ala Trp Pro
1               5                   10                  15

Ala Leu Ile Gln Leu Ile Ser Lys Thr Pro Cys Met Pro Gln Ala Ala
            20                  25                  30

Ser Asn Thr Ser Leu Gly Leu Gly Asp Leu Arg Val Pro Ser Ser Met
        35                  40                  45

Leu Tyr Trp Leu Phe Leu Pro Ser Ser Leu Leu Ala Ala Ala Thr Leu
    50                  55                  60

Ala Val Ser Pro Leu Leu Leu Val Thr Ile Leu Arg Asn Gln Arg Leu
65                  70                  75                  80

Arg Gln Glu Pro His Tyr Leu Leu Pro Ala Asn Ile Leu Leu Ser Asp
                85                  90                  95

Leu Ala Tyr Ile Leu Leu His Met Leu Ile Ser Ser Ser Ser Leu Gly
            100                 105                 110

Gly Trp Glu Leu Gly Arg Met Ala Cys Gly Ile Leu Thr Asp Ala Val
        115                 120                 125

Phe Ala Ala Cys Thr Ser Thr Ile Leu Ser Phe Thr Ala Ile Val Leu
    130                 135                 140

His Thr Tyr Leu Ala Val Ile His Pro Leu Arg Tyr Leu Ser Phe Met
145                 150                 155                 160

Ser His Gly Ala Ala Trp Lys Ala Val Ala Leu Ile Trp Leu Val Ala
                165                 170                 175
```

```
Cys Cys Phe Pro Thr Phe Leu Ile Trp Leu Ser Lys Trp Gln Asp Ala
            180                 185                 190

Gln Leu Glu Glu Gln Gly Ala Ser Tyr Ile Leu Pro Pro Ser Met Gly
        195                 200                 205

Thr Gln Pro Gly Cys Gly Leu Leu Val Ile Val Thr Tyr Thr Ser Ile
    210                 215                 220

Leu Cys Val Leu Phe Leu Cys Thr Ala Leu Ile Ala Asn Cys Phe Trp
225                 230                 235                 240

Arg Ile Tyr Ala Glu Ala Lys Thr Ser Gly Ile Trp Gly Gln Gly Tyr
                245                 250                 255

Ser Arg Ala Arg Gly Thr Leu Leu Ile His Ser Val Leu Ile Thr Leu
            260                 265                 270

Tyr Val Ser Thr Gly Val Val Phe Ser Leu Asp Met Val Leu Thr Arg
        275                 280                 285

Tyr His His Ile Asp Ser Gly Thr His Thr Trp Leu Leu Ala Ala Asn
    290                 295                 300

Ser Glu Val Leu Met Met Leu Pro Arg Ala Met Leu Pro Tyr Leu Tyr
305                 310                 315                 320

Leu Leu Arg Tyr Arg Gln Leu Leu Gly Met Val Arg Gly His Leu Pro
                325                 330                 335

Ser Arg Arg His Gln Ala Ile Phe Thr Ile Ser
            340                 345
```

<210> 39
<211> 1023
<212> DNA
<213> Homo sapiens

<400> 39

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atgaatccat ttcatgcatc ttgttggaac acctctgccg aacttttaaa caaatcctgg      60

aataaagagt ttgcttatca aactgccagt gtggtagata cagtcatcct cccttccatg     120

attgggatta tctgttcaac agggctggtt ggcaacatcc tcattgtatt cactataata     180

agatccagga aaaaaacagt ccctgacatc tatatctgca acctggctgt ggctgatttg     240

gtccacatag ttggaatgcc ttttcttatt caccaatggg cccgaggggg agagtgggtg     300

tttggggggc ctctctgcac catcatcaca tccctggata cttgtaacca atttgcctgt     360

agtgccatca tgactgtaat gagtgtggac aggtactttg ccctcgtcca accatttcga     420

ctgacacgtt ggagaacaag gtacaagacc atccggatca atttgggcct ttgggcagct     480

tcctttatcc tggcattgcc tgtctgggtc tactcgaagg tcatcaaatt taaagacggt     540

gttgagagtt gtgcttttga tttgacatcc cctgacgatg tactctggta tacactttat     600

ttgacgataa caactttttt tttccctcta cccttgattt tggtgtgcta tattttaatt     660

ttatgctata cttgggagat gtatcaacag aataaggatg ccagatgctg caatcccagt     720

gtaccaaaac agagagtgat gaagttgaca aagatggtgc tggtgctggt ggtagtcttt     780
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atcctgagtg ctgcccctta tcatgtgata caactggtga acttacagat ggaacagccc 840

acactggcct tctatgtggg ttattacctc tccatctgtc tcagctatgc cagcagcagc 900

attaaccctt ttctctacat cctgctgagt ggaaatttcc agaaacgtct gcctcaaatc 960

caaagaagag cgactgagaa ggaaatcaac aatatgggaa acactctgaa atcacacttt 1020

tag 1023

<210> 40
<211> 340
<212> PRT
<213> Homo sapiens

<400> 40

Met Asn Pro Phe His Ala Ser Cys Trp Asn Thr Ser Ala Glu Leu Leu
1 5 10 15

Asn Lys Ser Trp Asn Lys Glu Phe Ala Tyr Gln Thr Ala Ser Val Val
20 25 30

Asp Thr Val Ile Leu Pro Ser Met Ile Gly Ile Ile Cys Ser Thr Gly
35 40 45

Leu Val Gly Asn Ile Leu Ile Val Phe Thr Ile Ile Arg Ser Arg Lys
50 55 60

Lys Thr Val Pro Asp Ile Tyr Ile Cys Asn Leu Ala Val Ala Asp Leu
65 70 75 80

Val His Ile Val Gly Met Pro Phe Leu Ile His Gln Trp Ala Arg Gly
85 90 95

Gly Glu Trp Val Phe Gly Gly Pro Leu Cys Thr Ile Ile Thr Ser Leu
100 105 110

Asp Thr Cys Asn Gln Phe Ala Cys Ser Ala Ile Met Thr Val Met Ser
115 120 125

Val Asp Arg Tyr Phe Ala Leu Val Gln Pro Phe Arg Leu Thr Arg Trp
130 135 140

Arg Thr Arg Tyr Lys Thr Ile Arg Ile Asn Leu Gly Leu Trp Ala Ala
145 150 155 160

Ser Phe Ile Leu Ala Leu Pro Val Trp Val Tyr Ser Lys Val Ile Lys
165 170 175

Phe Lys Asp Gly Val Glu Ser Cys Ala Phe Asp Leu Thr Ser Pro Asp
180 185 190

Asp Val Leu Trp Tyr Thr Leu Tyr Leu Thr Ile Thr Thr Phe Phe Phe
195 200 205

Pro Leu Pro Leu Ile Leu Val Cys Tyr Ile Leu Ile Leu Cys Tyr Thr
210 215 220

Trp Glu Met Tyr Gln Gln Asn Lys Asp Ala Arg Cys Cys Asn Pro Ser
225 230 235 240

Val Pro Lys Gln Arg Val Met Lys Leu Thr Lys Met Val Leu Val Leu

```
                245                 250                 255

Val Val Val Phe Ile Leu Ser Ala Ala Pro Tyr His Val Ile Gln Leu
            260                 265                 270

Val Asn Leu Gln Met Glu Gln Pro Thr Leu Ala Phe Tyr Val Gly Tyr
        275                 280                 285

Tyr Leu Ser Ile Cys Leu Ser Tyr Ala Ser Ser Ser Ile Asn Pro Phe
    290                 295                 300

Leu Tyr Ile Leu Leu Ser Gly Asn Phe Gln Lys Arg Leu Pro Gln Ile
305                 310                 315                 320

Gln Arg Arg Ala Thr Glu Lys Glu Ile Asn Asn Met Gly Asn Thr Leu
                325                 330                 335

Lys Ser His Phe
            340

<210>  41
<211>  24
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence


<400>  41
cttgcagaca tcaccatggc agcc                                             24


<210>  42
<211>  24
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence


<400>  42
gtgatgctct gagtactgga ctgg                                             24


<210>  43
<211>  20
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence


<400>  43
gaagctgtga agagtgatgc                                                  20


<210>  44
<211>  24
<212>  DNA
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<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 44
gtcagcaata ttgataagca gcag 24

<210> 45
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 45
ccatggggaa cgattctgtc agctacg 27

<210> 46
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 46
gctatgcctg aagccagtct tgtg 24

<210> 47
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 47
ccaggatgtt gtgtcaccgt ggtggc 26

<210> 48
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 48
cacagcgctg cagccctgca gctggc 26

<210> 49
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 49
cttcctctcg tagggatgaa ccagac 26

<210> 50
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 50
ctcgcacagg tgggaagcac ctgtgg 26

<210> 51
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 51
gcctgtgaca ggaggtaccc tgg 23

<210> 52
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 52
catatccctc cgagtgtcca gcggc 25

<210> 53
<211> 31
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature

<223> Novel Sequence

<400> 53
gcatggagag aaaatttatg tccttgcaac c 31

<210> 54
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 54
caagaacagg tctcatctaa gagctcc 27

<210> 55
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 55
gctgttgcca tgacgtccac ctgcac 26

<210> 56
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 56
ggacagttca aggtttgcct tagaac 26

<210> 57
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 57
ctttcgatac tgctcctatg ctc 23

<210> 58
<211> 26

<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 58
gtagtccact gaaagtccag tgatcc 26

<210> 59
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 59
tttctgagca tggatccaac catctc 26

<210> 60
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 60
ctgtctgaca gggcagaggc tcttc 25

<210> 61
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 61
ggaactcgta tagacccagc gtcgctcc 28

<210> 62
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 62

ggaggttgcg ccttagcgac agatgacc 28

<210> 63
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 63
ctgcacccgg acacttgctc tg 22

<210> 64
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 64
gtctgcttgt tcagtgccac tcaac 25

<210> 65
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 65
tatctgcaat tctattctag ctcctg 26

<210> 66
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 66
tgtccctaat aaagtcacat gaatgc 26

<210> 67
<211> 23
<212> DNA
<213> Artificial Sequence

<220>

<221> misc_feature
<223> Novel Sequence

<400> 67
ggagacaacc atgaatgagc cac 23

<210> 68
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 68
tatttcaagg gttgtttgag taac 24

<210> 69
<211> 27
<212> DNA
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<220>
<221> misc_feature
<223> Novel Sequence

<400> 69
ggcaccagtg gaggttttct gagcatg 27

<210> 70
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 70
ctgatggaag tagaggctgt ccatctc 27

<210> 71
<211> 23
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 71
cctggcgagc cgctagcgcc atg 23

<210> 72

<211> 23
<212> DNA
<213> Artificial Sequence

<220>
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<223> Novel Sequence

<400> 72
atgagccctg ccaggccctc agt 23

<210> 73
<211> 27
<212> DNA
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<220>
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<400> 73
ctgcgatgcc cacactcaat acttctg 27

<210> 74
<211> 27
<212> DNA
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<220>
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<223> Novel Sequence

<400> 74
aaggatccta cacttggtgg atctcag 27

<210> 75
<211> 22
<212> DNA
<213> Artificial Sequence

<400> 75
gctggagcat tcactaggcg ag 22

<210> 76
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
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<223> Novel Sequence

<400> 76
agatcctggt tcttggtgac aatg 24

<210> 77

<211> 24
<212> DNA
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<220>
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<223> Novel Sequence

<400> 77
agccatccct gccaggaagc atgg 24

<210> 78
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 78
ccagactgtg gactcaagaa ctctagg 27

<210> 79
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 79
agtccacgaa caatgaatcc atttcatg 28

<210> 80
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 80
atcatgtcta gactcatggt gatcc 25

<210> 81
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 81
ggggagggaa agcaaaggtg gtcctcctgg 30

<210> 82
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 82
ccaggagaac cacctttgct ttccctcccc 30

<210> 83
<211> 1356
<212> DNA
<213> Homo sapiens

<400> 83
atggagtcct cacccatccc ccagtcatca gggaactctt ccactttggg gagggtccct 60

caaaccccag gtccctctac tgccagtggg gtcccggagg tggggctacg ggatgttgct 120

tcggaatctg tggccctctt cttcatgctc ctgctggact tgactgctgt ggctggcaat 180

gccgctgtga tggccgtgat cgccaagacg cctgccctcc gaaaatttgt cttcgtcttc 240

cacctctgcc tggtggacct gctggctgcc ctgaccctca tgcccctggc catgctctcc 300

agctctgccc tctttgacca cgccctcttt ggggaggtgg cctgccgcct ctacttgttt 360

ctgagcgtgt gctttgtcag cctggccatc ctctcggtgt cagccatcaa tgtggagcgc 420

tactattacg tagtccaccc catgcgctac gaggtgcgca tgacgctggg gctggtggcc 480

tctgtgctgg tgggtgtgtg ggtgaaggcc ttggccatgg cttctgtgcc agtgttggga 540

agggtctcct gggaggaagg agctcccagt gtcccccccag gctgttcact ccagtggagc 600

cacagtgcct actgccagct tttgtggtgg gtctttgctg tcctttactt tctgttgccc 660

ctgctcctca tacttgtggt ctactgcagc atgttccgag tggcccgcgt ggctgccatg 720

cagcacgggc cgctgcccac gtggatggag acaccccggc aacgctccga atctctcagc 780

agccgctcca cgatggtcac cagctcgggg gccccccaga ccaccccaca ccggacgttt 840

gggggaggga aagcaaaggt ggttctcctg gctgtggggg gacagttcct gctctgttgg 900

ttgccctact tctctttcca cctctatgtt gccctgagtg ctcagcccat ttcaactggg 960

caggtggaga gtgtggtcac ctggattggc tacttttgct tcacttccaa ccctttcttc 1020

tatggatgtc tcaaccggca gatccggggg gagctcagca agcagtttgt ctgcttcttc 1080

aagccagctc cagaggagga gctgaggctg cctagccggg agggctccat tgaggagaac 1140

ttcctgcagt tccttcaggg gactggctgt ccttctgagt cctgggtttc ccgaccccta 1200

cccagcccca agcaggagcc acctgctgtt gactttcgaa tcccaggcca gatagctgag 1260

gagacctctg agttcctgga gcagcaactc accagcgaca tcatcatgtc agacagctac 1320

ctccgtcctg ccgcctcacc ccggctggag tcatga 1356

<210> 84
<211> 451
<212> PRT
<213> Homo sapiens

<400> 84

Met Glu Ser Ser Pro Ile Pro Gln Ser Ser Gly Asn Ser Ser Thr Leu
1 5 10 15

Gly Arg Val Pro Gln Thr Pro Gly Pro Ser Thr Ala Ser Gly Val Pro
20 25 30

Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
35 40 45

Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
50 55 60

Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
65 70 75 80

His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
85 90 95

Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
100 105 110

Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
115 120 125

Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
130 135 140

Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
145 150 155 160

Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
165 170 175

Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
180 185 190

Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
195 200 205

Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Leu Ile
210 215 220

Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
225 230 235 240

Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
245 250 255

Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
260 265 270

Gln Thr Thr Pro His Arg Thr Phe Gly Gly Gly Lys Ala Lys Val Val

```
        275                 280                 285

Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe
    290                 295                 300

Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly
305                 310                 315                 320

Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser
                325                 330                 335

Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu
            340                 345                 350

Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu
        355                 360                 365

Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe
    370                 375                 380

Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu
385                 390                 395                 400

Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly
                405                 410                 415

Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser
            420                 425                 430

Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg
        435                 440                 445

Leu Glu Ser
    450
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<210> 85
<211> 28
<212> DNA
<213> Homo sapiens

<400> 85
caggaaggca aagaccacca tcatcatc 28

<210> 86
<211> 28
<212> DNA
<213> Homo sapiens

<400> 86
gatgatgatg gtggtctttg ccttcctg 28

<210> 87
<211> 1041
<212> DNA
<213> Homo sapiens

<400> 87
atggagagaa aatttatgtc cttgcaacca tccatctccg tatcagaaat ggaaccaaat 60

ggcaccttca gcaataacaa cagcaggaac tgcacaattg aaaacttcaa gagagaattt 120

ttcccaattg tatatctgat aatatttttc tggggagtct tgggaaatgg gttgtccata 180

tatgttttcc tgcagcctta taagaagtcc acatctgtga acgttttcat gctaaatctg 240

gccatttcag atctcctgtt cataagcacg cttcccttca gggctgacta ttatcttaga 300

ggctccaatt ggatatttgg agacctggcc tgcaggatta tgtcttattc cttgtatgtc 360

aacatgtaca gcagtattta tttcctgacc gtgctgagtg ttgtgcgttt cctggcaatg 420

gttcacccct ttcggcttct gcatgtcacc agcatcagga gtgcctggat cctctgtggg 480

atcatatgga tccttatcat ggcttcctca ataatgctcc tggacagtgg ctctgagcag 540

aacggcagtg tcacatcatg cttagagctg aatctctata aaattgctaa gctgcagacc 600

atgaactata ttgccttggt ggtgggctgc ctgctgccat ttttcacact cagcatctgt 660

tatctgctga tcattcgggt tctgttaaaa gtggaggtcc cagaatcggg gctgcgggtt 720

tctcacagga aggcaaagac caccatcatc atcaccttga tcatcttctt cttgtgtttc 780

ctgccctatc acacactgag gaccgtccac ttgacgacat ggaaagtggg tttatgcaaa 840

gacagactgc ataaagcttt ggttatcaca ctggccttgg cagcagccaa tgcctgcttc 900

aatcctctgc tctattactt tgctggggag aattttaagg acagactaaa gtctgcactc 960

agaaaaggcc atccacagaa ggcaaagaca aagtgtgttt tccctgttag tgtgtggttg 1020

agaaaggaaa caagagtata a 1041

<210> 88
<211> 346
<212> PRT
<213> Homo sapiens

<400> 88

Met Glu Arg Lys Phe Met Ser Leu Gln Pro Ser Ile Ser Val Ser Glu
1 5 10 15

Met Glu Pro Asn Gly Thr Phe Ser Asn Asn Asn Ser Arg Asn Cys Thr
20 25 30

Ile Glu Asn Phe Lys Arg Glu Phe Phe Pro Ile Val Tyr Leu Ile Ile
35 40 45

Phe Phe Trp Gly Val Leu Gly Asn Gly Leu Ser Ile Tyr Val Phe Leu
50 55 60

Gln Pro Tyr Lys Lys Ser Thr Ser Val Asn Val Phe Met Leu Asn Leu
65 70 75 80

Ala Ile Ser Asp Leu Leu Phe Ile Ser Thr Leu Pro Phe Arg Ala Asp
85 90 95

Tyr Tyr Leu Arg Gly Ser Asn Trp Ile Phe Gly Asp Leu Ala Cys Arg
100 105 110

Ile Met Ser Tyr Ser Leu Tyr Val Asn Met Tyr Ser Ser Ile Tyr Phe
115 120 125

Leu Thr Val Leu Ser Val Val Arg Phe Leu Ala Met Val His Pro Phe
130 135 140

```
Arg Leu Leu His Val Thr Ser Ile Arg Ser Ala Trp Ile Leu Cys Gly
145                 150                 155                 160

Ile Ile Trp Ile Leu Ile Met Ala Ser Ser Ile Met Leu Leu Asp Ser
                165                 170                 175

Gly Ser Glu Gln Asn Gly Ser Val Thr Ser Cys Leu Glu Leu Asn Leu
            180                 185                 190

Tyr Lys Ile Ala Lys Leu Gln Thr Met Asn Tyr Ile Ala Leu Val Val
        195                 200                 205

Gly Cys Leu Leu Pro Phe Phe Thr Leu Ser Ile Cys Tyr Leu Leu Ile
    210                 215                 220

Ile Arg Val Leu Leu Lys Val Glu Val Pro Glu Ser Gly Leu Arg Val
225                 230                 235                 240

Ser His Arg Lys Ala Lys Thr Thr Ile Ile Ile Thr Leu Ile Ile Phe
                245                 250                 255

Phe Leu Cys Phe Leu Pro Tyr His Thr Leu Arg Thr Val His Leu Thr
            260                 265                 270

Thr Trp Lys Val Gly Leu Cys Lys Asp Arg Leu His Lys Ala Leu Val
        275                 280                 285

Ile Thr Leu Ala Leu Ala Ala Ala Asn Ala Cys Phe Asn Pro Leu Leu
    290                 295                 300

Tyr Tyr Phe Ala Gly Glu Asn Phe Lys Asp Arg Leu Lys Ser Ala Leu
305                 310                 315                 320

Arg Lys Gly His Pro Gln Lys Ala Lys Thr Lys Cys Val Phe Pro Val
                325                 330                 335

Ser Val Trp Leu Arg Lys Glu Thr Arg Val
            340                 345

<210>  89
<211>  28
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence

<400>  89
ccagtgcaaa gctaagaaag tgatcttc                                          28

<210>  90
<211>  28
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence

<400>  90
gaagatcact ttcttagctt tgcactgg                                          28
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<210> 91
<211> 1527
<212> DNA
<213> Homo sapiens

<400> 91
atgacgtcca cctgcaccaa cagcacgcgc gagagtaaca gcagccacac gtgcatgccc 60

ctctccaaaa tgcccatcag cctggcccac ggcatcatcc gctcaaccgt gctggttatc 120

ttcctcgccg cctctttcgt cggcaacata gtgctggcgc tagtgttgca gcgcaagccg 180

cagctgctgc aggtgaccaa ccgttttatc tttaacctcc tcgtcaccga cctgctgcag 240

atttcgctcg tggccccctg ggtggtggcc acctctgtgc ctctcttctg gcccctcaac 300

agccacttct gcacggccct ggttagcctc acccacctgt tcgccttcgc cagcgtcaac 360

accattgtcg tggtgtcagt ggatcgctac ttgtccatca tccaccctct ctcctacccg 420

tccaagatga cccagcgccg cggttacctg ctcctctatg gcacctggat tgtggccatc 480

ctgcagagca ctcctccact ctacggctgg ggccaggctg cctttgatga gcgcaatgct 540

ctctgctcca tgatctgggg ggccagcccc agctacacta ttctcagcgt ggtgtccttc 600

atcgtcattc cactgattgt catgattgcc tgctactccg tggtgttctg tgcagcccgg 660

aggcagcatg ctctgctgta caatgtcaag agacacagct tggaagtgcg agtcaaggac 720

tgtgtggaga atgaggatga agagggagca gagaagaagg aggagttcca ggatgagagt 780

gagtttcgcc gccagcatga aggtgaggtc aaggccaagg agggcagaat ggaagccaag 840

gacggcagcc tgaaggccaa ggaaggaagc acggggacca gtgagagtag tgtagaggcc 900

aggggcagcg aggaggtcag agagagcagc acggtggcca gcgacggcag catggagggt 960

aaggaaggca gcaccaaagt tgaggagaac agcatgaagg cagacaaggg tcgcacagag 1020

gtcaaccagt gcagcattga cttgggtgaa gatgacatgg agtttggtga agacgacatc 1080

aatttcagtg aggatgacgt cgaggcagtg aacatcccgg agagcctccc acccagtcgt 1140

cgtaacagca acagcaaccc tcctctgccc aggtgctacc agtgcaaagc taagaaagtg 1200

atcttcatca tcattttctc ctatgtgcta tccctggggc cctactgctt tttagcagtc 1260

ctggccgtgt gggtggatgt cgaaacccag gtaccccagt gggtgatcac cataatcatc 1320

tggcttttct tcctgcagtg ctgcatccac ccctatgtct atggctacat gcacaagacc 1380

attaagaagg aaatccagga catgctgaag aagttcttct gcaaggaaaa gcccccgaaa 1440

gaagatagcc acccagacct gcccggaaca gagggtggga ctgaaggcaa gattgtccct 1500

tcctacgatt ctgctacttt tccttga 1527

<210> 92
<211> 508
<212> PRT
<213> Homo sapiens

<400> 92

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Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His
1               5                   10                  15

Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile
            20                  25                  30

Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly
        35                  40                  45

Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln
    50                  55                  60

Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln
65                  70                  75                  80

Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe
                85                  90                  95

Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His
            100                 105                 110

Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp
        115                 120                 125

Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr
    130                 135                 140

Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile
145                 150                 155                 160

Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp
                165                 170                 175

Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr
            180                 185                 190

Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
        195                 200                 205

Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
    210                 215                 220

Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
225                 230                 235                 240

Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
                245                 250                 255

Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
            260                 265                 270

Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
        275                 280                 285

Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
    290                 295                 300

Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
305                 310                 315                 320

Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
                325                 330                 335
```

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Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
            340                 345                 350

Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
        355                 360                 365

Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
    370                 375                 380

Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Lys Lys Val
385                 390                 395                 400

Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
                405                 410                 415

Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
            420                 425                 430

Gln Trp Val Ile Thr Ile Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
        435                 440                 445

Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
    450                 455                 460

Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
465                 470                 475                 480

Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
                485                 490                 495

Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro
            500                 505

<210>  93
<211>  29
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence


<400>  93
gccgccaccg cgccaagagg aagattggc                                          29


<210>  94
<211>  29
<212>  DNA
<213>  Artificial Sequence

<220>
<221>  misc_feature
<223>  Novel Sequence


<400>  94
gccaatcttc ctcttggcgc ggtggcggc                                          29


<210>  95
<211>  1092
<212>  DNA
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<213> Homo sapiens

<400> 95
atgggccccg gcgaggcgct gctggcgggt ctcctggtga tggtactggc cgtggcgctg 60

ctatccaacg cactggtgct gctttgttgc gcctacagcg ctgagctccg cactcgagcc 120

tcaggcgtcc tcctggtgaa tctgtcgctg ggccacctgc tgctggcggc gctggacatg 180

cccttcacgc tgctcggtgt gatgcgcggg cggacaccgt cggcgcccgg cgcatgccaa 240

gtcattggct tcctggacac cttcctggcg tccaacgcgg cgctgagcgt ggcggcgctg 300

agcgcagacc agtggctggc agtgggcttc ccactgcgct acgccggacg cctgcgaccg 360

cgctatgccg gcctgctgct gggctgtgcc tggggacagt cgctggcctt ctcaggcgct 420

gcacttggct gctcgtggct tggctacagc agcgccttcg cgtcctgttc gctgcgcctg 480

ccgccccgagc ctgagcgtcc gcgcttcgca gccttcaccg ccacgctcca tgccgtgggc 540

ttcgtgctgc cgctggcggt gctctgcctc acctcgctcc aggtgcaccg ggtggcacgc 600

agccactgcc agcgcatgga caccgtcacc atgaaggcgc tcgcgctgct cgccgacctg 660

caccccagtg tgcggcagcg ctgcctcatc cagcagaagc ggcgccgcca ccgcgccacc 720

aggaagattg gcattgctat tgcgaccttc ctcatctgct ttgccccgta tgtcatgacc 780

aggctggcgg agctcgtgcc cttcgtcacc gtgaacgccc agaagggcat cctcagcaag 840

tgcctgacct acagcaaggc ggtggccgac ccgttcacgt actctctgct ccgccggccg 900

ttccgccaag tcctggccgg catggtgcac cggctgctga agagaacccc gcgcccagca 960

tccacccatg acagctctct ggatgtggcc ggcatggtgc accagctgct gaagagaacc 1020

ccgcgcccag cgtccaccca caacggctct gtggacacag agaatgattc ctgcctgcag 1080

cagacacact ga 1092

<210> 96
<211> 363
<212> PRT
<213> Homo sapiens

<400> 96

Met Gly Pro Gly Glu Ala Leu Leu Ala Gly Leu Leu Val Met Val Leu
1 5 10 15

Ala Val Ala Leu Leu Ser Asn Ala Leu Val Leu Leu Cys Cys Ala Tyr
20 25 30

Ser Ala Glu Leu Arg Thr Arg Ala Ser Gly Val Leu Leu Val Asn Leu
35 40 45

Ser Leu Gly His Leu Leu Leu Ala Ala Leu Asp Met Pro Phe Thr Leu
50 55 60

Leu Gly Val Met Arg Gly Arg Thr Pro Ser Ala Pro Gly Ala Cys Gln
65 70 75 80

Val Ile Gly Phe Leu Asp Thr Phe Leu Ala Ser Asn Ala Ala Leu Ser

```
                85                  90                  95

Val Ala Ala Leu Ser Ala Asp Gln Trp Leu Ala Val Gly Phe Pro Leu
            100                 105                 110

Arg Tyr Ala Gly Arg Leu Arg Pro Arg Tyr Ala Gly Leu Leu Leu Gly
        115                 120                 125

Cys Ala Trp Gly Gln Ser Leu Ala Phe Ser Gly Ala Ala Leu Gly Cys
    130                 135                 140

Ser Trp Leu Gly Tyr Ser Ser Ala Phe Ala Ser Cys Ser Leu Arg Leu
145                 150                 155                 160

Pro Pro Glu Pro Glu Arg Pro Arg Phe Ala Ala Phe Thr Ala Thr Leu
                165                 170                 175

His Ala Val Gly Phe Val Leu Pro Leu Ala Val Leu Cys Leu Thr Ser
            180                 185                 190

Leu Gln Val His Arg Val Ala Arg Ser His Cys Gln Arg Met Asp Thr
        195                 200                 205

Val Thr Met Lys Ala Leu Ala Leu Leu Ala Asp Leu His Pro Ser Val
    210                 215                 220

Arg Gln Arg Cys Leu Ile Gln Gln Lys Arg Arg Arg His Arg Ala Thr
225                 230                 235                 240

Arg Lys Ile Gly Ile Ala Ile Ala Thr Phe Leu Ile Cys Phe Ala Pro
                245                 250                 255

Tyr Val Met Thr Arg Leu Ala Glu Leu Val Pro Phe Val Thr Val Asn
            260                 265                 270

Ala Gln Lys Gly Ile Leu Ser Lys Cys Leu Thr Tyr Ser Lys Ala Val
        275                 280                 285

Ala Asp Pro Phe Thr Tyr Ser Leu Leu Arg Arg Pro Phe Arg Gln Val
    290                 295                 300

Leu Ala Gly Met Val His Arg Leu Leu Lys Arg Thr Pro Arg Pro Ala
305                 310                 315                 320

Ser Thr His Asp Ser Ser Leu Asp Val Ala Gly Met Val His Gln Leu
                325                 330                 335

Leu Lys Arg Thr Pro Arg Pro Ala Ser Thr His Asn Gly Ser Val Asp
            340                 345                 350

Thr Glu Asn Asp Ser Cys Leu Gln Gln Thr His
        355                 360
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<220>
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<210> 98
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<212> DNA
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<220>
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<400> 98
gatcgatatc cgtgactcca gccggggtga ggcggc 36

<210> 99
<211> 2610
<212> DNA
<213> Homo sapiens and Rat

<400> 99
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tcggaatctg tggccctctt cttcatgctc ctgctggact tgactgctgt ggctggcaat 180

gccgctgtga tggccgtgat cgccaagacg cctgccctcc gaaaatttgt cttcgtcttc 240

cacctctgcc tggtggacct gctggctgcc ctgaccctca tgcccctggc catgctctcc 300

agctctgccc tctttgacca cgccctcttt ggggaggtgg cctgccgcct ctacttgttt 360

ctgagcgtgt gctttgtcag cctggccatc ctctcggtgt cagccatcaa tgtggagcgc 420

tactattacg tagtccaccc catgcgctac gaggtgcgca tgacgctggg gctggtggcc 480

tctgtgctgg tgggtgtgtg ggtgaaggcc ttggccatgg cttctgtgcc agtgttggga 540

agggtctcct gggaggaagg agctcccagt gtcccccag gctgttcact ccagtggagc 600

cacagtgcct actgccagct tttgtggtg gtctttgctg tcctttactt tctgttgccc 660

ctgctcctca tacttgtggt ctactgcagc atgttccgag tggcccgcgt ggctgccatg 720

cagcacgggc cgctgcccac gtggatggag acaccccggc aacgctccga atctctcagc 780

agccgctcca cgatggtcac cagctcgggg gcccccaga ccaccccaca ccggacgttt 840

gggggaggga aagcagcagt ggttctcctg gctgtggggg gacagttcct gctctgttgg 900

ttgccctact tctctttcca cctctatgtt gccctgagtg ctcagcccat ttcaactggg 960

caggtggaga gtgtggtcac ctggattggc tacttttgct tcacttccaa ccctttcttc 1020

tatggatgtc tcaaccggca gatccggggg gagctcagca agcagtttgt ctgcttcttc 1080

aagccagctc cagaggagga gctgaggctg cctagccggg agggctccat tgaggagaac 1140

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cccagcccca agcaggagcc acctgctgtt gactttcgaa tcccaggcca gatagctgag 1260

gagacctctg agttcctgga gcagcaactc accagcgaca tcatcatgtc agacagctac 1320

ctccgtcctg ccgcctcacc ccggctggag tcagcgatat ctgcagaatt ccaccacact 1380

ggactagtgg atccgagctc ggtaccaagc ttgggctgca ggtcgatggg ctgcctcggc 1440

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atcgagaagc agctgcagaa ggacaagcag gtctaccggg ccacgcaccg cctgctgctg 1560

ctgggtgctg gagagtctgg caaaagcacc attgtgaagc agatgaggat cctacatgtt 1620

aatgggttta acggagaggg cggcgaagag gacccgcagg ctgcaaggag caacagcgat 1680

ggtgagaagg ccaccaaagt gcaggacatc aaaaacaacc tgaaggaggc cattgaaacc 1740

attgtggccg ccatgagcaa cctggtgccc cccgtggagc tggccaaccc tgagaaccag 1800

ttcagagtgg actacattct gagcgtgatg aacgtgccaa actttgactt cccacctgaa 1860

ttctatgagc atgccaaggc tctgtgggag gatgagggag ttcgtgcctg ctacgagcgc 1920

tccaacgagt accagctgat cgactgtgcc cagtacttcc tggacaagat tgatgtgatc 1980

aagcaggccg actacgtgcc aagtgaccag gacctgcttc gctgccgcgt cctgacctct 2040

ggaatctttg agaccaagtt ccaggtggac aaagtcaact tccacatgtt cgatgtgggc 2100

ggccagcgcg atgaacgccg caagtggatc cagtgcttca atgatgtgac tgccatcatc 2160

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gccgtggaca ctgagaacat ccgccgtgtc ttcaacgact gccgtgacat catccagcgc 2580

atgcatcttc gccaatacga gctgctctaa 2610

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<212> PRT
<213> Homo sapiens and Rat

<400> 100

Met Glu Ser Ser Pro Ile Pro Gln Ser Ser Gly Asn Ser Ser Thr Leu
1 5 10 15

Gly Arg Val Pro Gln Thr Pro Gly Pro Ser Thr Ala Ser Gly Val Pro
20 25 30

Glu Val Gly Leu Arg Asp Val Ala Ser Glu Ser Val Ala Leu Phe Phe
35 40 45

Met Leu Leu Leu Asp Leu Thr Ala Val Ala Gly Asn Ala Ala Val Met
50 55 60

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Ala Val Ile Ala Lys Thr Pro Ala Leu Arg Lys Phe Val Phe Val Phe
65                  70                  75                  80

His Leu Cys Leu Val Asp Leu Leu Ala Ala Leu Thr Leu Met Pro Leu
                85                  90                  95

Ala Met Leu Ser Ser Ser Ala Leu Phe Asp His Ala Leu Phe Gly Glu
            100                 105                 110

Val Ala Cys Arg Leu Tyr Leu Phe Leu Ser Val Cys Phe Val Ser Leu
        115                 120                 125

Ala Ile Leu Ser Val Ser Ala Ile Asn Val Glu Arg Tyr Tyr Tyr Val
    130                 135                 140

Val His Pro Met Arg Tyr Glu Val Arg Met Thr Leu Gly Leu Val Ala
145                 150                 155                 160

Ser Val Leu Val Gly Val Trp Val Lys Ala Leu Ala Met Ala Ser Val
                165                 170                 175

Pro Val Leu Gly Arg Val Ser Trp Glu Glu Gly Ala Pro Ser Val Pro
            180                 185                 190

Pro Gly Cys Ser Leu Gln Trp Ser His Ser Ala Tyr Cys Gln Leu Phe
        195                 200                 205

Val Val Val Phe Ala Val Leu Tyr Phe Leu Leu Pro Leu Leu Leu Ile
    210                 215                 220

Leu Val Val Tyr Cys Ser Met Phe Arg Val Ala Arg Val Ala Ala Met
225                 230                 235                 240

Gln His Gly Pro Leu Pro Thr Trp Met Glu Thr Pro Arg Gln Arg Ser
                245                 250                 255

Glu Ser Leu Ser Ser Arg Ser Thr Met Val Thr Ser Ser Gly Ala Pro
            260                 265                 270

Gln Thr Thr Pro His Arg Thr Phe Gly Gly Gly Lys Ala Ala Val Val
        275                 280                 285

Leu Leu Ala Val Gly Gly Gln Phe Leu Leu Cys Trp Leu Pro Tyr Phe
    290                 295                 300

Ser Phe His Leu Tyr Val Ala Leu Ser Ala Gln Pro Ile Ser Thr Gly
305                 310                 315                 320

Gln Val Glu Ser Val Val Thr Trp Ile Gly Tyr Phe Cys Phe Thr Ser
                325                 330                 335

Asn Pro Phe Phe Tyr Gly Cys Leu Asn Arg Gln Ile Arg Gly Glu Leu
            340                 345                 350

Ser Lys Gln Phe Val Cys Phe Phe Lys Pro Ala Pro Glu Glu Glu Leu
        355                 360                 365

Arg Leu Pro Ser Arg Glu Gly Ser Ile Glu Glu Asn Phe Leu Gln Phe
    370                 375                 380

Leu Gln Gly Thr Gly Cys Pro Ser Glu Ser Trp Val Ser Arg Pro Leu
385                 390                 395                 400

Pro Ser Pro Lys Gln Glu Pro Pro Ala Val Asp Phe Arg Ile Pro Gly
                405                 410                 415
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Gln Ile Ala Glu Glu Thr Ser Glu Phe Leu Glu Gln Gln Leu Thr Ser
420 425 430

Asp Ile Ile Met Ser Asp Ser Tyr Leu Arg Pro Ala Ala Ser Pro Arg
435 440 445

Leu Glu Ser Ala Ile Ser Ala Glu Phe His His Thr Gly Leu Val Asp
450 455 460

Pro Ser Ser Val Pro Ser Leu Gly Cys Arg Ser Met Gly Cys Leu Gly
465 470 475 480

Asn Ser Lys Thr Glu Asp Gln Arg Asn Glu Glu Lys Ala Gln Arg Glu
485 490 495

Ala Asn Lys Lys Ile Glu Lys Gln Leu Gln Lys Asp Lys Gln Val Tyr
500 505 510

Arg Ala Thr His Arg Leu Leu Leu Leu Gly Ala Gly Glu Ser Gly Lys
515 520 525

Ser Thr Ile Val Lys Gln Met Arg Ile Leu His Val Asn Gly Phe Asn
530 535 540

Gly Glu Gly Gly Glu Glu Asp Pro Gln Ala Ala Arg Ser Asn Ser Asp
545 550 555 560

Gly Glu Lys Ala Thr Lys Val Gln Asp Ile Lys Asn Asn Leu Lys Glu
565 570 575

Ala Ile Glu Thr Ile Val Ala Ala Met Ser Asn Leu Val Pro Pro Val
580 585 590

Glu Leu Ala Asn Pro Glu Asn Gln Phe Arg Val Asp Tyr Ile Leu Ser
595 600 605

Val Met Asn Val Pro Asn Phe Asp Phe Pro Pro Glu Phe Tyr Glu His
610 615 620

Ala Lys Ala Leu Trp Glu Asp Glu Gly Val Arg Ala Cys Tyr Glu Arg
625 630 635 640

Ser Asn Glu Tyr Gln Leu Ile Asp Cys Ala Gln Tyr Phe Leu Asp Lys
645 650 655

Ile Asp Val Ile Lys Gln Ala Asp Tyr Val Pro Ser Asp Gln Asp Leu
660 665 670

Leu Arg Cys Arg Val Leu Thr Ser Gly Ile Phe Glu Thr Lys Phe Gln
675 680 685

Val Asp Lys Val Asn Phe His Met Phe Asp Val Gly Gly Gln Arg Asp
690 695 700

Glu Arg Arg Lys Trp Ile Gln Cys Phe Asn Asp Val Thr Ala Ile Ile
705 710 715 720

Phe Val Val Ala Ser Ser Ser Tyr Asn Met Val Ile Arg Glu Asp Asn
725 730 735

Gln Thr Asn Arg Leu Gln Glu Ala Leu Asn Leu Phe Lys Ser Ile Trp
740 745 750

Asn Asn Arg Trp Leu Arg Thr Ile Ser Val Ile Leu Phe Leu Asn Lys

755 760 765

Gln Asp Leu Leu Ala Glu Lys Val Leu Ala Gly Lys Ser Lys Ile Glu
770 775 780

Asp Tyr Phe Pro Glu Phe Ala Arg Tyr Thr Thr Pro Glu Asp Ala Thr
785 790 795 800

Pro Glu Pro Gly Glu Asp Pro Arg Val Thr Arg Ala Lys Tyr Phe Ile
805 810 815

Arg Asp Glu Phe Leu Arg Ile Ser Thr Ala Ser Gly Asp Gly Arg His
820 825 830

Tyr Cys Tyr Pro His Phe Thr Cys Ala Val Asp Thr Glu Asn Ile Arg
835 840 845

Arg Val Phe Asn Asp Cys Arg Asp Ile Ile Gln Arg Met His Leu Arg
850 855 860

Gln Tyr Glu Leu Leu
865

<210> 101
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 101
tctagaatga cgtccacctg caccaacagc 30

<210> 102
<211> 34
<212> DNA
<213> Artificial Sequence

<220>
<221> misc_feature
<223> Novel Sequence

<400> 102
gatatcgcag gaaaagtagc agaatcgtag gaag 34

<210> 103
<211> 2781
<212> DNA
<213> Homo Sapiens and Rat

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ctctccaaaa tgcccatcag cctggcccac ggcatcatcc gctcaaccgt gctggttatc 120

ttcctcgccg cctctttcgt cggcaacata gtgctggcgc tagtgttgca gcgcaagccg 180

cagctgctgc aggtgaccaa ccgttttatc tttaacctcc tcgtcaccga cctgctgcag 240

atttcgctcg tggccccctg ggtggtggcc acctctgtgc ctctcttctg gcccctcaac 300
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gactacattc tgagcgtgat gaacgtgcca aactttgact tcccacctga attctatgag 2040
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taccagctga tcgactgtgc ccagtacttc ctggacaaga ttgatgtgat caagcaggcc 2160
gactacgtgc caagtgacca ggacctgctt cgctgccgcg tcctgacctc tggaatcttt 2220

gagaccaagt tccaggtgga caaagtcaac ttccacatgt tcgatgtggg cggccagcgc 2280

gatgaacgcc gcaagtggat ccagtgcttc aatgatgtga ctgccatcat cttcgtggtg 2340

gccagcagca gctacaacat ggtcatccgg gaggacaacc agaccaaccg tctgcaggag 2400

gctctgaacc tcttcaagag catctggaac aacagatggc tgcgtaccat ctctgtgatc 2460

ctcttcctca acaagcaaga tctgcttgct gagaaggtcc tcgctgggaa atcgaagatt 2520

gaggactact ttccagagtt cgctcgctac accactcctg aggatgcgac tcccgagccc 2580

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agcactgcta gtggagatgg acgtcactac tgctaccctc actttacctg cgccgtggac 2700

actgagaaca tccgccgtgt cttcaacgac tgccgtgaca tcatccagcg catgcatctt 2760

cgccaatacg agctgctcta a 2781

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<211> 926
<212> PRT
<213> Homo sapiens and Rat

<400> 104

Met Thr Ser Thr Cys Thr Asn Ser Thr Arg Glu Ser Asn Ser Ser His
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Thr Cys Met Pro Leu Ser Lys Met Pro Ile Ser Leu Ala His Gly Ile
20 25 30

Ile Arg Ser Thr Val Leu Val Ile Phe Leu Ala Ala Ser Phe Val Gly
35 40 45

Asn Ile Val Leu Ala Leu Val Leu Gln Arg Lys Pro Gln Leu Leu Gln
50 55 60

Val Thr Asn Arg Phe Ile Phe Asn Leu Leu Val Thr Asp Leu Leu Gln
65 70 75 80

Ile Ser Leu Val Ala Pro Trp Val Val Ala Thr Ser Val Pro Leu Phe
85 90 95

Trp Pro Leu Asn Ser His Phe Cys Thr Ala Leu Val Ser Leu Thr His
100 105 110

Leu Phe Ala Phe Ala Ser Val Asn Thr Ile Val Val Val Ser Val Asp
115 120 125

Arg Tyr Leu Ser Ile Ile His Pro Leu Ser Tyr Pro Ser Lys Met Thr
130 135 140

Gln Arg Arg Gly Tyr Leu Leu Leu Tyr Gly Thr Trp Ile Val Ala Ile
145 150 155 160

Leu Gln Ser Thr Pro Pro Leu Tyr Gly Trp Gly Gln Ala Ala Phe Asp
165 170 175

Glu Arg Asn Ala Leu Cys Ser Met Ile Trp Gly Ala Ser Pro Ser Tyr
180 185 190

Thr Ile Leu Ser Val Val Ser Phe Ile Val Ile Pro Leu Ile Val Met
195 200 205

Ile Ala Cys Tyr Ser Val Val Phe Cys Ala Ala Arg Arg Gln His Ala
210 215 220

Leu Leu Tyr Asn Val Lys Arg His Ser Leu Glu Val Arg Val Lys Asp
225 230 235 240

Cys Val Glu Asn Glu Asp Glu Glu Gly Ala Glu Lys Lys Glu Glu Phe
245 250 255

Gln Asp Glu Ser Glu Phe Arg Arg Gln His Glu Gly Glu Val Lys Ala
260 265 270

Lys Glu Gly Arg Met Glu Ala Lys Asp Gly Ser Leu Lys Ala Lys Glu
275 280 285

Gly Ser Thr Gly Thr Ser Glu Ser Ser Val Glu Ala Arg Gly Ser Glu
290 295 300

Glu Val Arg Glu Ser Ser Thr Val Ala Ser Asp Gly Ser Met Glu Gly
305 310 315 320

Lys Glu Gly Ser Thr Lys Val Glu Glu Asn Ser Met Lys Ala Asp Lys
325 330 335

Gly Arg Thr Glu Val Asn Gln Cys Ser Ile Asp Leu Gly Glu Asp Asp
340 345 350

Met Glu Phe Gly Glu Asp Asp Ile Asn Phe Ser Glu Asp Asp Val Glu
355 360 365

Ala Val Asn Ile Pro Glu Ser Leu Pro Pro Ser Arg Arg Asn Ser Asn
370 375 380

Ser Asn Pro Pro Leu Pro Arg Cys Tyr Gln Cys Lys Ala Ala Lys Val
385 390 395 400

Ile Phe Ile Ile Ile Phe Ser Tyr Val Leu Ser Leu Gly Pro Tyr Cys
405 410 415

Phe Leu Ala Val Leu Ala Val Trp Val Asp Val Glu Thr Gln Val Pro
420 425 430

Gln Trp Val Ile Thr Ile Ile Ile Trp Leu Phe Phe Leu Gln Cys Cys
435 440 445

Ile His Pro Tyr Val Tyr Gly Tyr Met His Lys Thr Ile Lys Lys Glu
450 455 460

Ile Gln Asp Met Leu Lys Lys Phe Phe Cys Lys Glu Lys Pro Pro Lys
465 470 475 480

Glu Asp Ser His Pro Asp Leu Pro Gly Thr Glu Gly Gly Thr Glu Gly
485 490 495

Lys Ile Val Pro Ser Tyr Asp Ser Ala Thr Phe Pro Ala Ile Ser Ala
500 505 510

Glu Phe His His Thr Gly Leu Val Asp Pro Ser Ser Val Pro Ser Leu
515 520 525

Gly Cys Arg Ser Met Gly Cys Leu Gly Asn Ser Lys Thr Glu Asp Gln
530 535 540

Arg Asn Glu Glu Lys Ala Gln Arg Glu Ala Asn Lys Lys Ile Glu Lys
545 550 555 560

Gln Leu Gln Lys Asp Lys Gln Val Tyr Arg Ala Thr His Arg Leu Leu
565 570 575

Leu Leu Gly Ala Gly Glu Ser Gly Lys Ser Thr Ile Val Lys Gln Met
580 585 590

Arg Ile Leu His Val Asn Gly Phe Asn Gly Glu Gly Gly Glu Glu Asp
595 600 605

Pro Gln Ala Ala Arg Ser Asn Ser Asp Gly Glu Lys Ala Thr Lys Val
610 615 620

Gln Asp Ile Lys Asn Asn Leu Lys Glu Ala Ile Glu Thr Ile Val Ala
625 630 635 640

Ala Met Ser Asn Leu Val Pro Pro Val Glu Leu Ala Asn Pro Glu Asn
645 650 655

Gln Phe Arg Val Asp Tyr Ile Leu Ser Val Met Asn Val Pro Asn Phe
660 665 670

Asp Phe Pro Pro Glu Phe Tyr Glu His Ala Lys Ala Leu Trp Glu Asp
675 680 685

Glu Gly Val Arg Ala Cys Tyr Glu Arg Ser Asn Glu Tyr Gln Leu Ile
690 695 700

Asp Cys Ala Gln Tyr Phe Leu Asp Lys Ile Asp Val Ile Lys Gln Ala
705 710 715 720

Asp Tyr Val Pro Ser Asp Gln Asp Leu Leu Arg Cys Arg Val Leu Thr
725 730 735

Ser Gly Ile Phe Glu Thr Lys Phe Gln Val Asp Lys Val Asn Phe His
740 745 750

Met Phe Asp Val Gly Gly Gln Arg Asp Glu Arg Arg Lys Trp Ile Gln
755 760 765

Cys Phe Asn Asp Val Thr Ala Ile Ile Phe Val Val Ala Ser Ser Ser
770 775 780

Tyr Asn Met Val Ile Arg Glu Asp Asn Gln Thr Asn Arg Leu Gln Glu
785 790 795 800

Ala Leu Asn Leu Phe Lys Ser Ile Trp Asn Asn Arg Trp Leu Arg Thr
805 810 815

Ile Ser Val Ile Leu Phe Leu Asn Lys Gln Asp Leu Leu Ala Glu Lys
820 825 830

Val Leu Ala Gly Lys Ser Lys Ile Glu Asp Tyr Phe Pro Glu Phe Ala
835 840 845

Arg Tyr Thr Thr Pro Glu Asp Ala Thr Pro Glu Pro Gly Glu Asp Pro
850 855 860

Arg Val Thr Arg Ala Lys Tyr Phe Ile Arg Asp Glu Phe Leu Arg Ile
865 870 875 880

Ser Thr Ala Ser Gly Asp Gly Arg His Tyr Cys Tyr Pro His Phe Thr

885 890 895

Cys Ala Val Asp Thr Glu Asn Ile Arg Arg Val Phe Asn Asp Cys Arg
900 905 910

Asp Ile Ile Gln Arg Met His Leu Arg Gln Tyr Glu Leu Leu
915 920 925

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<210> 106
<211> 24
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<400> 106
gctatgcctg aagccagtct tgtg 24

<210> 107
<211> 25
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<220>
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<400> 107
gcacctgctc ctgagcacct tctcc 25

<210> 108
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cacagcgctg cagccctgca gctggc 26

<210> 109

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<400> 109
ccagtgatga ctctgtccag cctg 24

<210> 110
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<400> 110
cagacacttg gcagggacga ggtg 24

<210> 111
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<400> 111
cttgtggtct actgcagcat gttccg 26

<210> 112
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<400> 112
catatccctc cgagtgtcca gcggc 25

<210> 113
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<400> 113
atggatcctt atcatggctt cctc 24

<210> 114
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<212> DNA
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<220>
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<400> 114
caagaacagg tctcatctaa gagctcc 27

<210> 115
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<220>
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<400> 115
ctctgatgcc atctgctgga ttcctg 26

<210> 116
<211> 26
<212> DNA
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<220>
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<400> 116
gtagtccact gaaagtccag tgatcc 26

<210> 117
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tggtggcgat ggccaacagc gctc 24

<210> 118
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<400> 118
gttgcgcctt agcgacagat gacc 24

<210> 119
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<400> 119
tcaacctgta tagcagcatc ctc 23

<210> 120
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<400> 120
aaggagtagc agaatggtta gcc 23

<210> 121
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<400> 121
gacacctgtc agcggtcgtg tgtg 24

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Thr Leu Glu Ser Ile Met
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Cys Gly Thr Gly Cys Thr Gly Cys Cys Thr Gly Ala Gly Cys Gly Ala
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Gly Gly Ala Gly
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Gly Ala Thr Cys Gly Gly Ala Thr Cys Cys Thr Thr Ala Gly Ala Ala
1 5 10 15

Cys Ala Gly Gly Cys Cys Gly Cys Ala Gly Thr Cys Cys Thr Thr Cys
20 25 30

Ala Gly Gly Thr Thr Cys Ala Gly Cys Thr Gly Cys Ala Gly Gly Ala
35 40 45

Thr Gly Gly Thr Gly
50